Ready Access to Carbazole and Carboline Functionality

A thesis submitted for the degree of Master of Philosophy
of the Australian National University

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National
University

Research School of Chemistry
Canberra, Australia

August 2019

Declaration

I declare that, to the best of my knowledge, the material presented in this Thesis represents the result of original work carried out by the author during the period 2012-2015 and has not been presented for examination for any other degree. This Thesis is less than 60,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Emma Gin

August 2019

Acknowledgements

I would like to thank the Australian National University Chemistry department for accepting me as a research student. Special thanks to Dr Martin Banwell, Dr Benoit Bolte, Dr Gottfried Otting, Dr Lara Malins, and in particular, Dr Tristan Reekie for your support in completing this milestone.

I am very grateful for the support and friendship of my coworkers in the school and laboratory – the time spent in Canberra would not be the same without you. Gratitude must also be extended to Dr. Chris Fitchett for setting me on a path of endless curiosity.

I wish to thank my family and friends for their love, never-ending support, and encouragement through all the years. I am forever grateful for your guidance, patience and kindness with me.

The financial support of the Australian Postgraduate Award, Alan Sargeson Merit Scholarship and the Research School of Chemistry Scholarship is also gratefully acknowledged.

Publications and Presentations

The following list details the publications and presentations that have resulted from research performed during the period of candidature

Publications

i) Q Yan, E Gin, M, Wasinska-Kalwa, MG Banwell, PD Carr (2017). A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A, *J. Org Chem*, 82(8), 4148–4159.

ii) Q Yan, E Gin, MG Banwell, AC Willis, PD Carr (2017). A Unified Approach to the Isomeric *α*-, *β*-, *γ*-, and *δ*-Carbolines via their 6,7,8,9-Tetrahydro Counterparts, *J. Org Chem*, 82(8), 4328–4335.

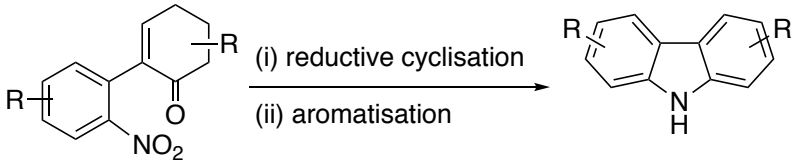
Presentations

i) E Gin and MG Banwell, *The Pd[0]-catalysed Ullmann Cross-coupling Route to Carbazoles*, **Poster Presentation**: Annual One-Day Symposium, Royal Australian Chemical Institute, Australian National University, Canberra, ACT, 2014.

Abstract

This thesis consists of two scientific articles and is preceded by an overview that contextualises the published work.

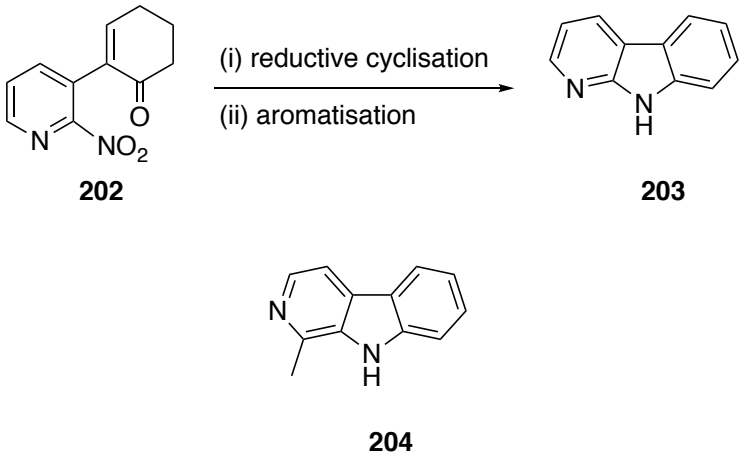
The first part of this thesis is comprised of Publication 1 and its corresponding supporting information. It is concerned with the synthesis of compounds of type **200** with various R substitutions utilising the Pd-catalysed Ullmann cross-coupling. Subjecting these compounds to a reductive cyclisation followed by aromatisation generates carbazoles **201** with various substitution patterns (**Scheme 34**). This methodology was also used to generate natural products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A



200 **201**

Scheme 34 Summary of Publication 1, a new synthetic approach to carbazoles.

The second part of the thesis is comprised of Publication 2 and its corresponding supporting information that builds upon the above-mentioned publication, where we were able to generate compound **202**. Subjecting this compound to a reductive cyclisation followed by aromatisation generates α-carboline **203** (**Scheme 35**). Compound **202** as its various *N*-regioisomers were also synthesised allowing access to β-, γ-, and δ-carbolines. This methodology was also used to generate natural product, β-carboline containing harman (**204**).



202 **203** **204**

Scheme 35 Summary of Publication 2, a new synthetic approach to carbolines.

Australian National University

February 2020

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title and authors: Q Yan, E Gin, M Wasinska-Kalwa, M G Banwell, PD Carr (2017). A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A

Current status of paper: Published

Contribution to paper: I assembled a body of original research by virtue of establishing synthetic pathways to all of the target carbazoles. In so doing, I performed an extensive series of new experiments and produced a substantial range of relevant data. These studies were refined and extended by Dr Qiao Yan so as to generate a data set suitable for publication.

Senior author or collaborating authors endorsement:

M. G. Banwell

Martin Banwell

Emma Gin		2/02/2020
Candidate – Print Name	Signature	Date

Endorsed

Lara Malins		3/2/20
Chair of Supervisory Panel – Print Name	Signature	Date
Gottfried Otting		3/2/20
Delegated Authority – Print Name	Signature	Date

Australian National University

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Title and authors: Q Yan, E Gin, MG Banwell, AC Willis, PD Carr (2017). A Unified Approach to the Isomeric α-, β-, γ-, and δ-Carbolines via their 6,7,8,9-Tetrahydro Counterparts

Current status of paper: Published

Contribution to paper: I was the co-worker who pursued the initial extension of the group's earlier work (including my own) on the synthesis of carbazoles to the corresponding carbolines. I made fundamental intellectual and experimental contributions to the opening stages of this work that was brought to publishable conclusions by Dr Qiao Yan.

Senior author or collaborating authors endorsement:

M. G. Banwell

Martin Banwell

Emma Gin		2/02/2020
Candidate – Print Name	Signature	Date

Endorsed

Lara Malins		3/2/20
Chair of Supervisory Panel – Print Name	Signature	Date
Gottfried Otting		3/2/20
Delegated Authority – Print Name	Signature	Date

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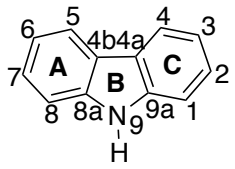
1. Chapter One. Introduction: Ready Access to Carbazole and Carboline Functionality Introduction

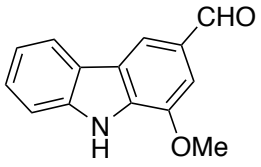
1.1 Carbazoles

9*H*-Carbazole (**Figure 1**, compound **1**) was first isolated from the anthracene fraction of coal tar distillate in 1872 by Grabe and Glaser.[1] In 1965, the first carbazole-containing natural product, murrayanine (**Figure 1**, compound **2**) was isolated from the plant *Murraya koenigii* Spreng. (Fam. Rutaceae).[2-3] The antimicrobial properties associated with murrayanine have generated great interest in the development of pathways to carbazole alkaloid synthesis. Since then, carbazole-containing compounds including natural products **3**,[4] **4**[5] and **5**,[6-7] have continued to inspire synthetic chemists. This is due to their intriguing structural features and manifold biological activities, which include antitumor, antibacterial, psychotropic, anti-inflammatory, antihistaminic, antimicrobial, anti-oxidative and antifungal properties, as well as antimalarial activity, further illustrating the medicinal relevance of carbazole chemistry. The carbazole moiety is therefore considered a pivotal pharmacophore for the development of new therapeutic agents. Examples of drugs that embody this motif include carvedilol (**6**)[8] and carazolol (**7**),[9] which are used to treat hypertension, ischemic heart disease and congestive heart failure. In addition to the vast array of biological activities, certain carbazoles also display properties likely to be of value in optoelectric materials, conducting polymers and synthetic dyes.



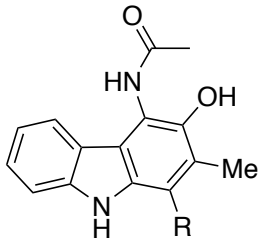
1
9*H*-carbazole

Representative carbazole-containing natural products



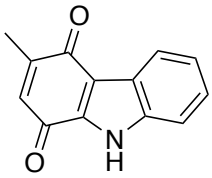
2

murrayanine
shows antimicrobial actions
against human pathogenic fungi

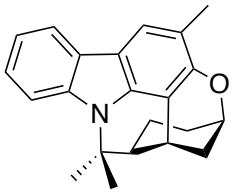


3

antiostatin A
shows strong inhibitory activity
against free radical-induced
lipid peroxidation

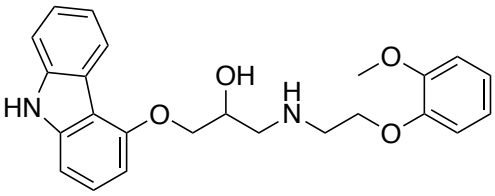


4
murrayaquinone A
induces myocardial contraction

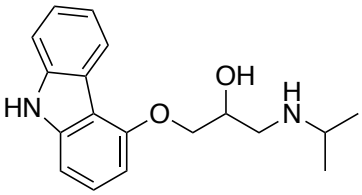


5
(+)-murrayazoline
exhibits potent antiplatelet
aggregation activity

Carbazole-containing pharmaceuticals



6
Carvedilol
non-selective beta blocker/alpha-1 blocker
used in the treatement of mild to severe congestive heart
failure and high blood pressure



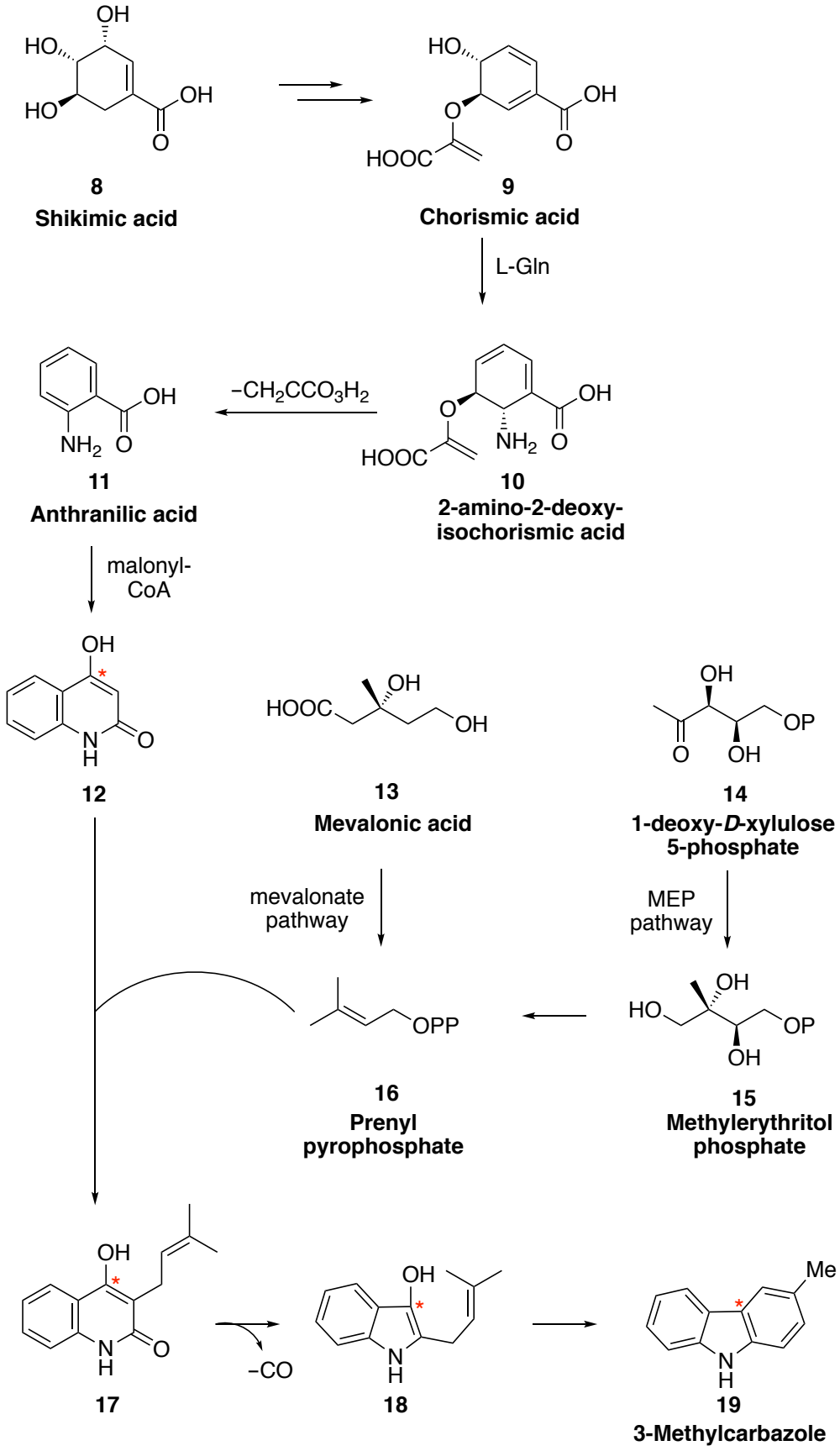
7
Carazolol
high affinity antagonist/beta blocker of
β-adrenergic receptor

Figure 1 Representative carbazole-containing compounds and some biological properties.

1.2 Biogenesis of the Carbazole Framework

The biosynthesis of the carbazole framework is not well known, but the so-called "anthranilic acid pathway", which proceeds via 3-prenylquinolone (**17**) to form the precursor compound 3-methylcarbazole (**19**), represents the most widely accepted proposal for the formation in higher plants (**Scheme 1**). This hypothesis is supported by the isolation of a range of carbazole alkaloids with a carbon centre formed from 3-dehydroquinic acid (**12**), (carbon centre labelled in **Scheme 1)** by a sequence of dehydration and reduction steps that take place within the developing carbazole framework.[10]

The biogenesis of the natural product 3-methylcarbazole as shown in **Scheme 1**, begins with shikimic acid (**8**).[3] ATP-dependent phosphorylation of shikimic acid (**8**) gives shikimic acid 3-phosphate which combines with phosphoenolpyruvate (PEP) via an addition-elimination reaction giving 3-enolpyruvylshikimic acid 3-phosphate (EPSP). 1,4-Elimination of phosphoric acid from EPSP leads to chorismic acid (**9**). Amination of chorismic acid (**9**) at C2 by L-glutamine (L-Gln) with elimination of water leads to 2-amino-2-deoxyisochorismic acid (**10**) and then anthranilic acid (**11**) following aromatisation. Anthraniloyl-coenzyme A (CoA), obtained from anthranilic acid and acetyl-coenzyme A (CoA), effects a chain extension to give the quinolone **12** via the addition of one molecule of malonyl-CoA through amide formation. Quinolone **12**, which later forms the indole unit of the carbazole framework, is then alkylated at the nucleophilic C3 position with prenyl pyrophosphate (**16**), affording 3-prenylquinoline (**17**). Prenyl pyrophosphate can be formed via two independent pathways depending on the organism: the mevalonate pathway in which prenyl pyrophosphate (**16**) is derived from mevalonic acid (**13**), or via the methylerythritol pathway (MEP) where prenyl pyrophosphate (**16**) is synthesised from 1-deoxy-D-xylulose (**14**) via methylerythritol phosphate (**15**). Mammals and fungi use the mevalonate pathway exclusively, while both can operate in plants, algae, and bacteria. The final step of the biosynthesis is thought to proceed via extrusion of carbon monoxide and subsequent oxidative cyclisation of the intermediate 2-prenylindole (**18**) to give 3-methylcarbazole (**19**).[3]



Scheme 1 Biogenesis of 3-methylcarbazole 19 via the "anthranilic acid pathway"

1.3. Established Methods for the Synthesis of Carbazoles

Numerous routes to the tricyclic carbazole framework have been developed and representative approaches are outlined in the following section.

Following conventional protocols, the three rings within the carbazole framework are labelled as A, B and C (**Figure 1**).

Accordingly, the synthesis of carbazoles can be divided into three classes:

1. The annulation of a benzenoid A or C ring to a substituted indole
2. A modular construction made involving the stepwise (or simultaneous introduction) of each ring (A + B + C or some variation thereof)
3. The construction of the central pyrrole (B) ring from a biphenyl derivative that therefore embodies the A and C rings.

1.3.1 The Annulation of a Benzenoid A or C ring to a Substituted Indole

The synthesis of carbazole from a substituted indole precursor can be classified as the annulation of either the A or C ring from an established indole core. Either the A or C ring can be synthesised from analogous precursors using similar chemistry, with differences only in the substitution pattern of the precursors (denoted by the R groups, **Figure 2**). For the purposes of the present discussion, the annulation of either the A or C ring to an indole core are considered equivalent.

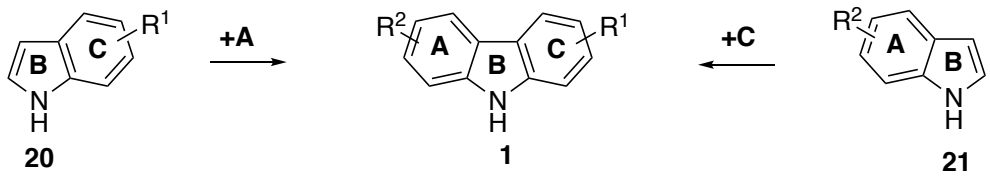
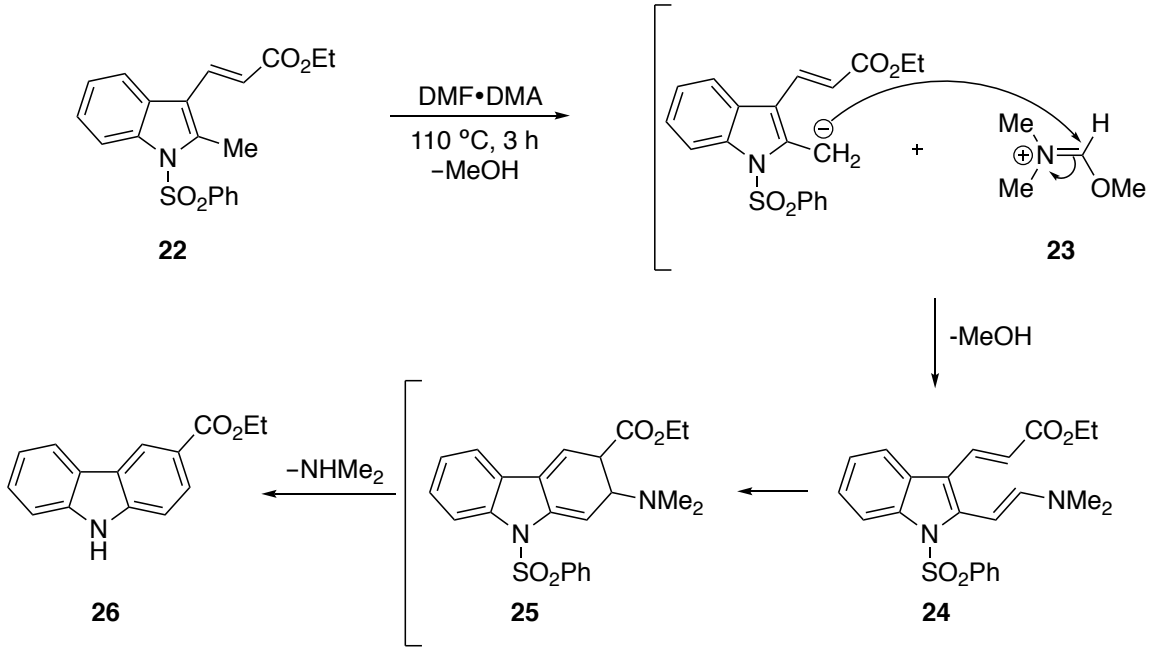


Figure 2 Synthesis of optionally "A or C" benzenoid rings from substituted indole derivatives

1.3.1.1 Electrocyclisation of Enamino Indole Precursors

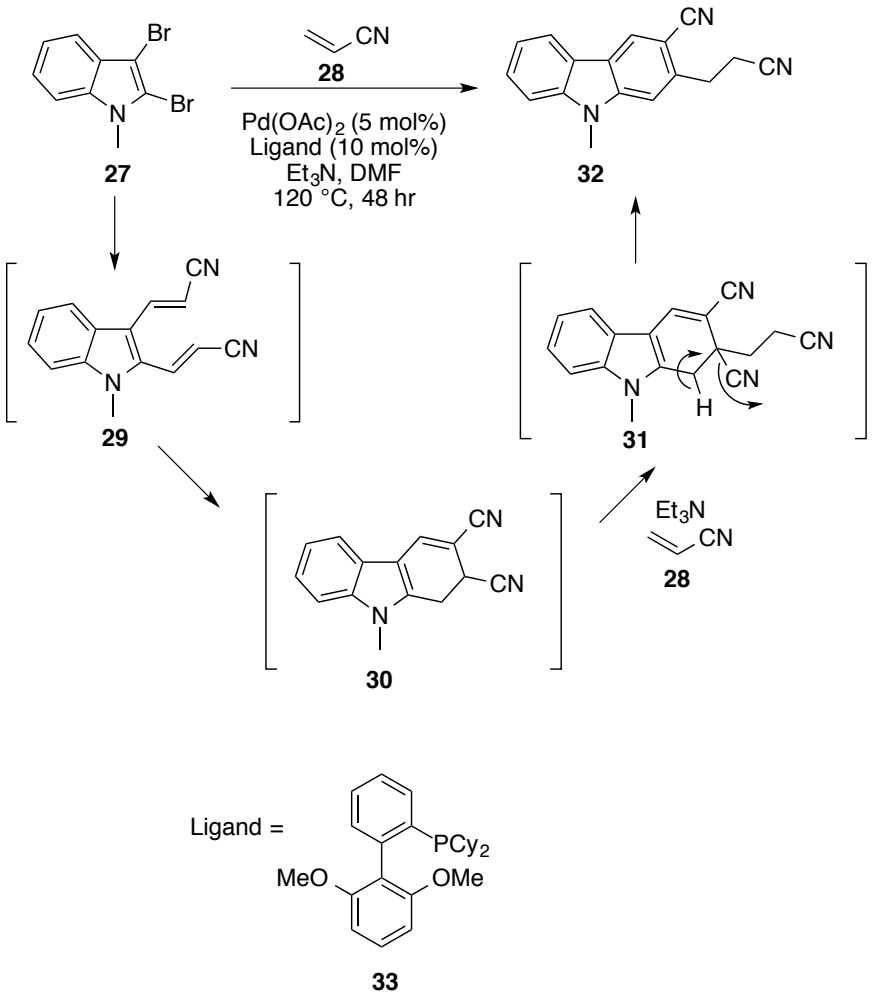
Mohanakrishnan and co-workers developed a route to functionalised carbazoles via electrocyclisation of an *in situ*-generated 2,3-dialkenylindole **24** (**Scheme 2**).[11-13] Firstly, 1-phenylsulfonyl-2-methyl-3-vinylindole (**22**) reacts with the cationic species **23**, which is generated by extrusion of methanol from DMF·DMA (dimethyl formamide·dimethyl acetal) or DMA·DMA (dimethyl acetamide·dimethyl acetal) at 110 ºC, leading to the formation of compound **24**. *N*-Protection is necessary for the electrocyclisation of 2,3-dialkenylindole systems as the electron withdrawing phenylsulfonyl group on the indole nitrogen provides triene character to the 2,3-divinylindole system. The mechanism can be understood through the electrocyclisation of intermediate enamine **24** followed by aromatisation of the resulting dihydrocarbazole **25** via elimination of dimethylamine to give the observed carbazole **26**.



Scheme 2 Electrocyclisation of enamines to give carbazoles

1.3.1.2 Palladium-catalysed Electrocyclisation of Dialkenylindole Derivatives

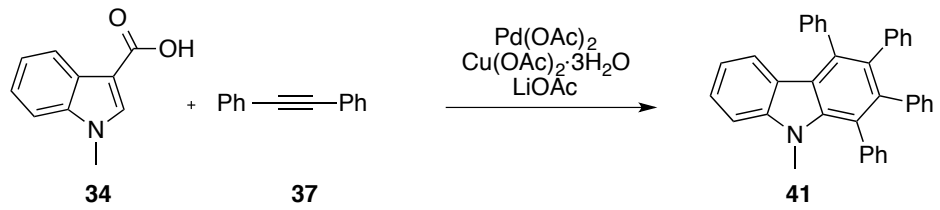
Langer *et. al* developed methods for the synthesis of carbazoles first involving a double-barrelled Heck reaction followed by an electrocyclisation to build the tricyclic 1,2-dihydrocarbazole motif.[14-15] For example, 2,3-dibromo-*N*-methylindole (**27**) and acrylonitrile (**28**) react via a double Heck reaction to give triene intermediate **29** (**Scheme 3**). A subsequent electrocyclic ring closure and oxidation gives the tricyclic 1,2-dihydrocarbazole intermediate **30**. Addition of another equivalent of acrylonitrile **28** in the presence of a base and subsequent aromatisation by elimination of hydrogen cyanide gives the carbazole **32**. When HCN cannot be eliminated, these intermediates can be converted to the corresponding carbazoles following dehydrogenation with Pd/C (10 mol %) in xylenes.



Scheme 3 Synthesis of carbazole via successive two-fold Heck and 6π-electrocyclisation reactions

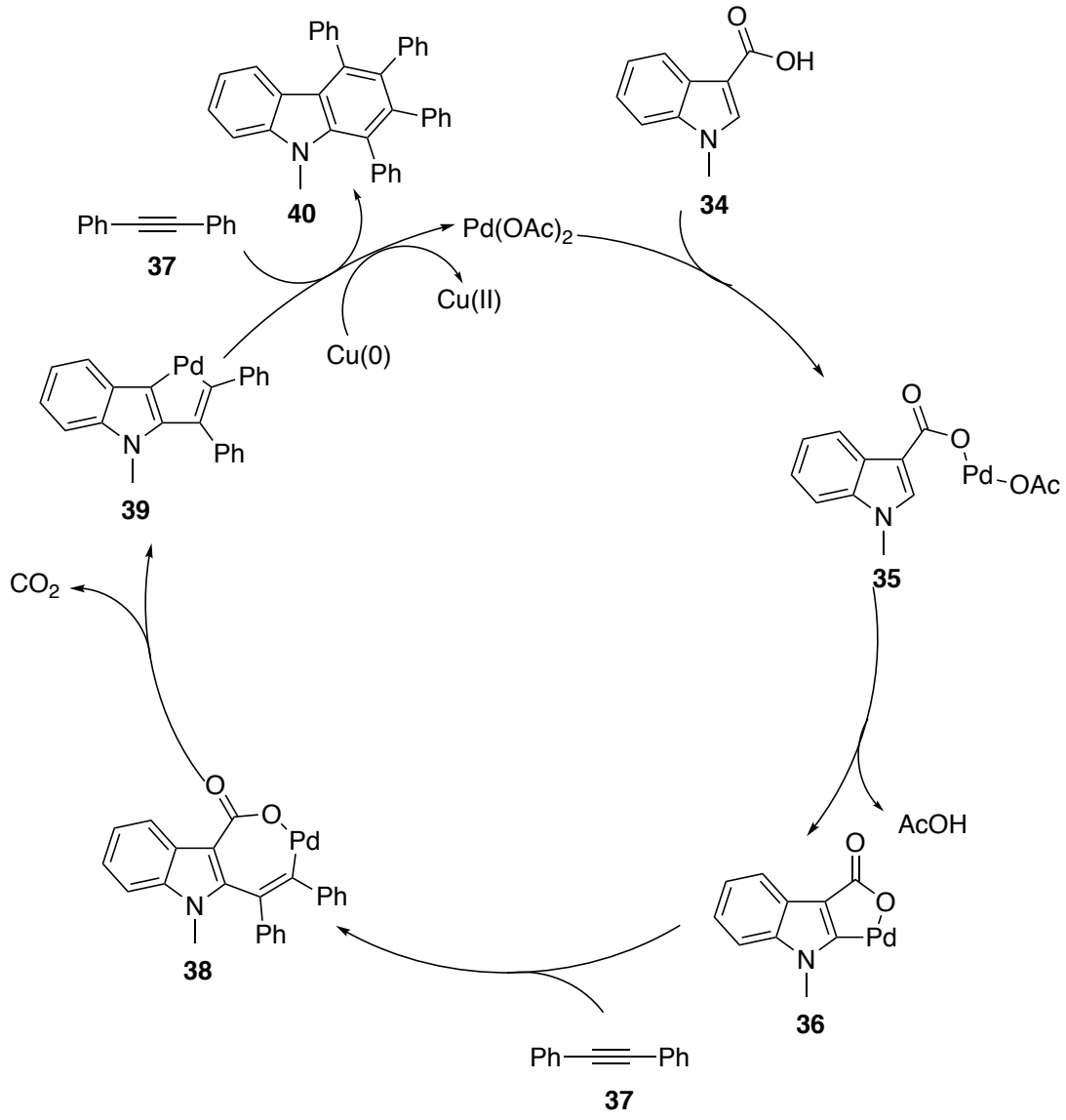
1.3.1.3 Palladium-catalysed Oxidative Cycloadditions of Indoles with Alkynes

Miura, Satoh and co-workers reported the synthesis of 1,2,3,4-tetrasubstituted carbazoles (e.g. **41**) through the palladium-catalysed oxidative coupling of *N*-substituted indoles and/or the corresponding carboxylic acid derivatives (**34**) with alkynes (**37**) using $Pd(OAc)_2$ as the catalyst, $Cu(OAc)_2 \cdot 3H_2O$ as the stoichiometric oxidant and LiOAc as an additive (**Scheme 4**).[16-17] The copper[II] salt oxidises the Pd[0] species to regenerate $Pd(OAc)_2$. One possible role of added LiOAc is to provide acetate anions as ligands to prevent the deactivation of Pd[0] through formation of insoluble metal species.



Scheme 4 Pd-catalysed oxidative coupling of 1-methylindole-3-carboxylic acid with an alkyne

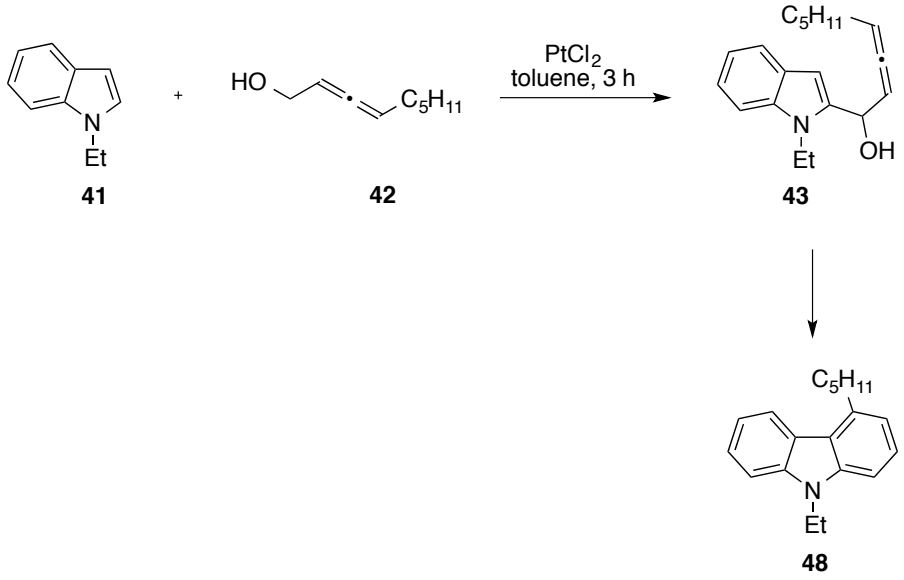
A possible mechanism for this conversion is shown in **Scheme 5**. Coordination of the carboxyl oxygen of compound **34** to $Pd(OAc)_2$ with liberation of acetic acid gives a palladium(II) carboxylate **35**, which undergoes directed palladation at the indole C2 position to give the palladacycle **36**. Subsequent alkyne insertion and decarboxylation then gives compound **39**. A second alkyne insertion followed by a reductive elimination affords the observed carbazole **40** and generates Pd[0], which is converted back to Pd[II] in the presence of $Cu(OAc)_2$.



Scheme 5 Possible mechanism for Pd-catalysed oxidative coupling of 1-methylindole-3-carboxylic acid (**34**) with alkynes such as (**37**)

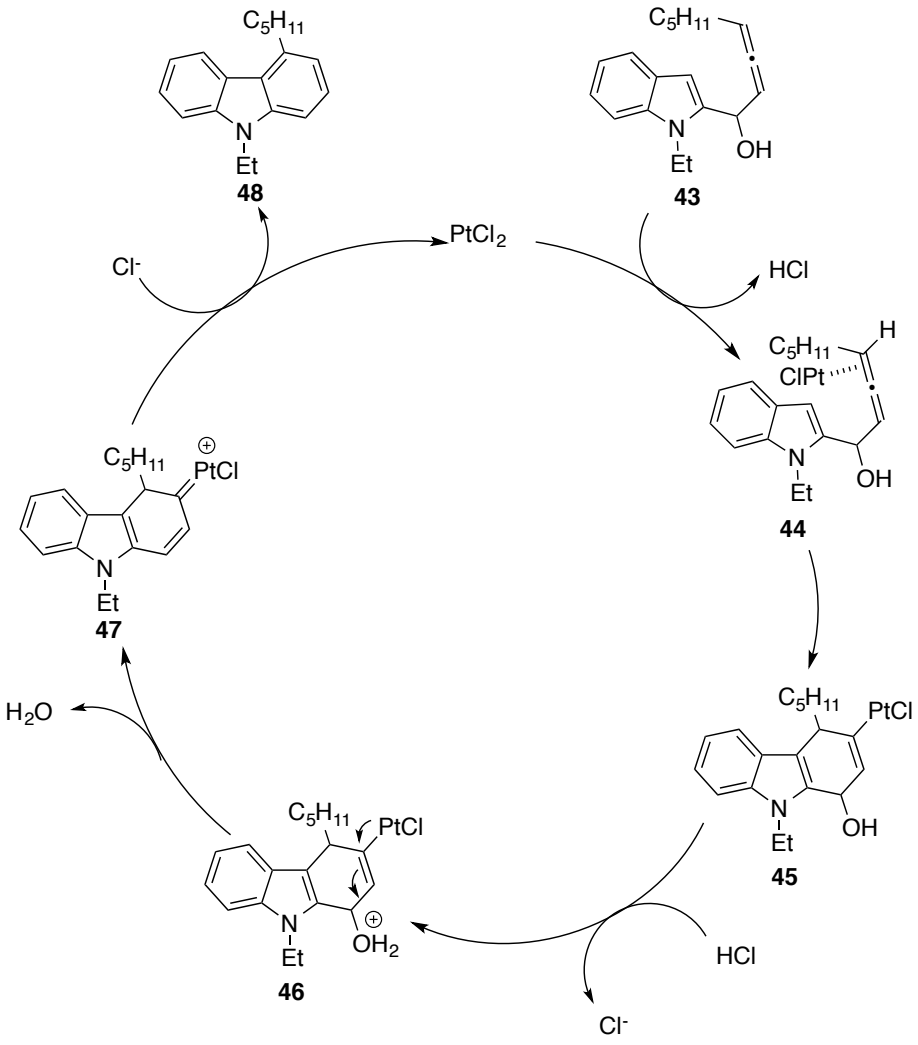
1.3.1.4 Platinum-catalysed Cyclisations of Indole-allenols

Kong and co-workers developed a method to synthesise substituted carbazoles that involves the $PtCl_2$-catalysed cyclisation of indol-2-yl-2,3-allenols such as **43** (**Scheme 6**).[18] The reaction of indole **41** and allene **42** gives indol-2-yl-2,3-allenol **43**, which then undergoes cyclisation under $PtCl_2$ catalysis to give the observed carbazole **48**.



Scheme 6 Pt(II)-catalysed cyclisation of 1-(indol-2-yl)-2,3-allenols from indoles to carbazoles

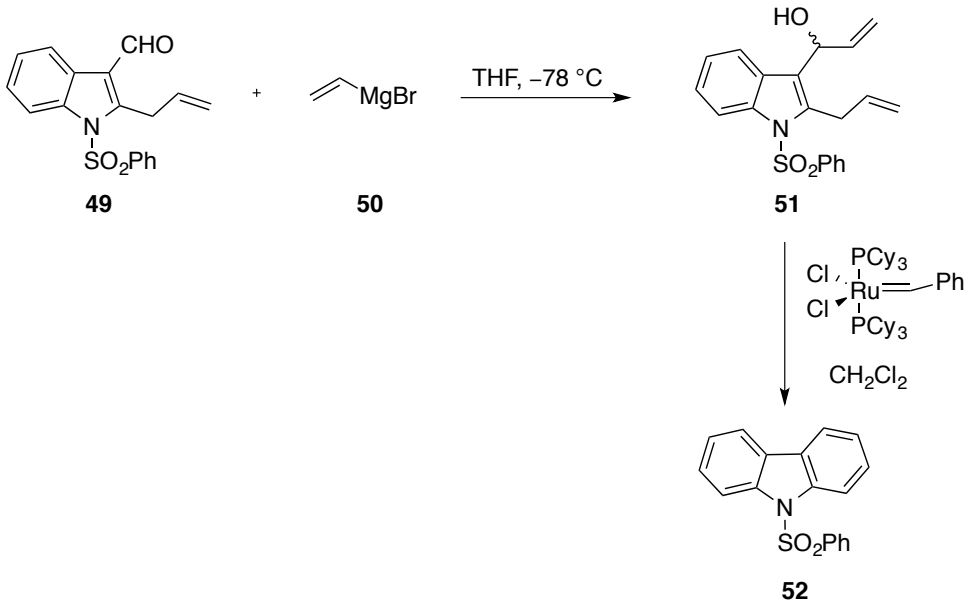
A possible mechanism involving a metal carbenoid intermediate **47** is shown in **Scheme 7**. Reaction of $PtCl_2$ with indole **43** is presumed to begin with coordination of the allene moiety to the platinum catalyst. Nucleophilic attack of the indole C3 onto the metal-activated electrophilic carbon double bond generates intermediate **45**. Protonation of the hydroxyl group followed by elimination of H_2O in intermediate **46** affords the cyclic platinum carbenoid **47**. A 1,2-H shift of intermediate **47** gives the observed product **48**, with concurrent regeneration of the catalyst $PtCl_2$.



Scheme 7 Proposed mechanism for Pt(II)-catalysed cyclisation of 1-(indol-2-yl)-2,3-allenols to carbazoles

1.3.1.5 Ring-closing Metathesis

Ring-closing metathesis (RCM) has become a widely adopted approach for carbon-carbon bond formation, especially in the synthesis of cyclic compounds (**Scheme 8**). Bennasar *et. al* have exploited such an approach to carbazole **52**.[19-20] First, the indole-3-carboxaldehyde **49** was treated with vinylmagnesium bromide **50** to generate diene **51**, which then participates in a Grubbs I-catalysed RCM reaction. Dehydrative aromatisation of the primary product of this reaction gives carbazole **52**.



Scheme 8 Synthesis of carbazole using ring-closing metathesis

1.3.2 A + B + C → ABC Routes to Carbazoles

Carbazoles can also be prepared from monocyclic precursors through the sequential introduction of the remaining rings (**Figure 3**).

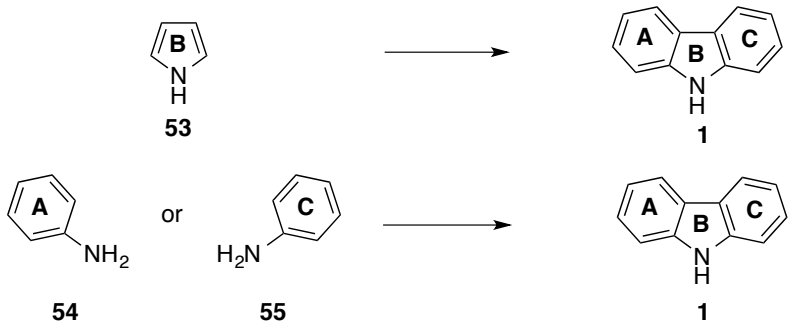
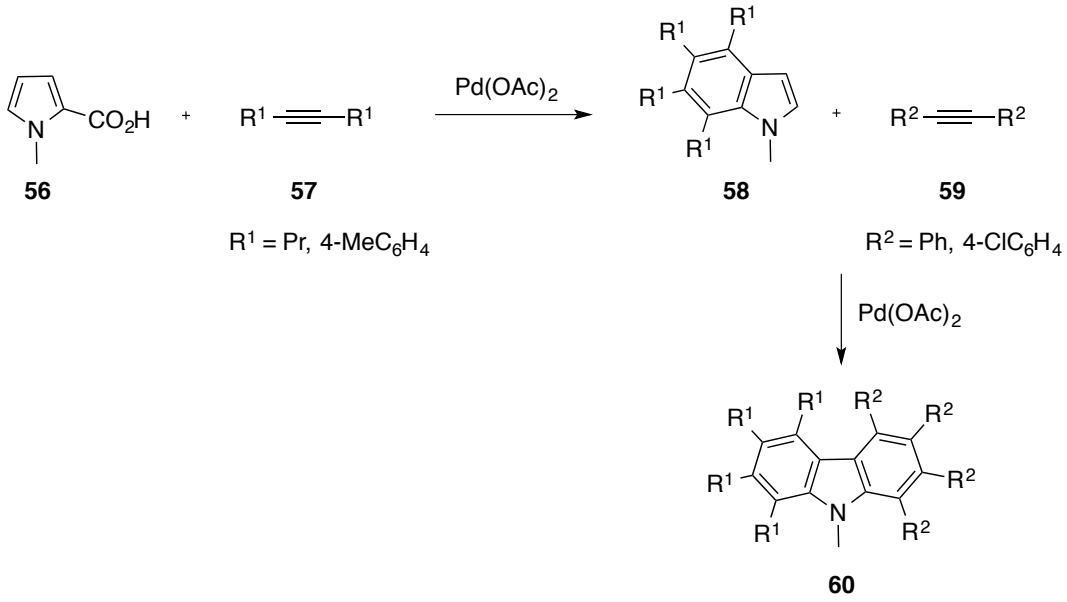


Figure 3 Formation of carbazoles in a modular-type sequence

1.3.2.1 Double Annulation via Palladium-catalysed Oxidative Cycloadditions with Alkynes

The palladium-catalysed oxidative cycloaddition of alkynes with indoles reported by Miura, Satoh *et al.* as described in the previous section (**Scheme 4**), can be extended to a

double annulation approach (**Scheme 9**).[16-17] Thus, stepwise couplings of 1-methylpyrrole-2-carboxylic acid (**56**) with two different alkynes such as **57** and **59** resulted in unsymmetrical and fully substituted carbazoles **60** via the formation of intermediate tetrasubstituted indole **58**. The mechanism of this transformation is closely related to that outlined in **Scheme 5**.

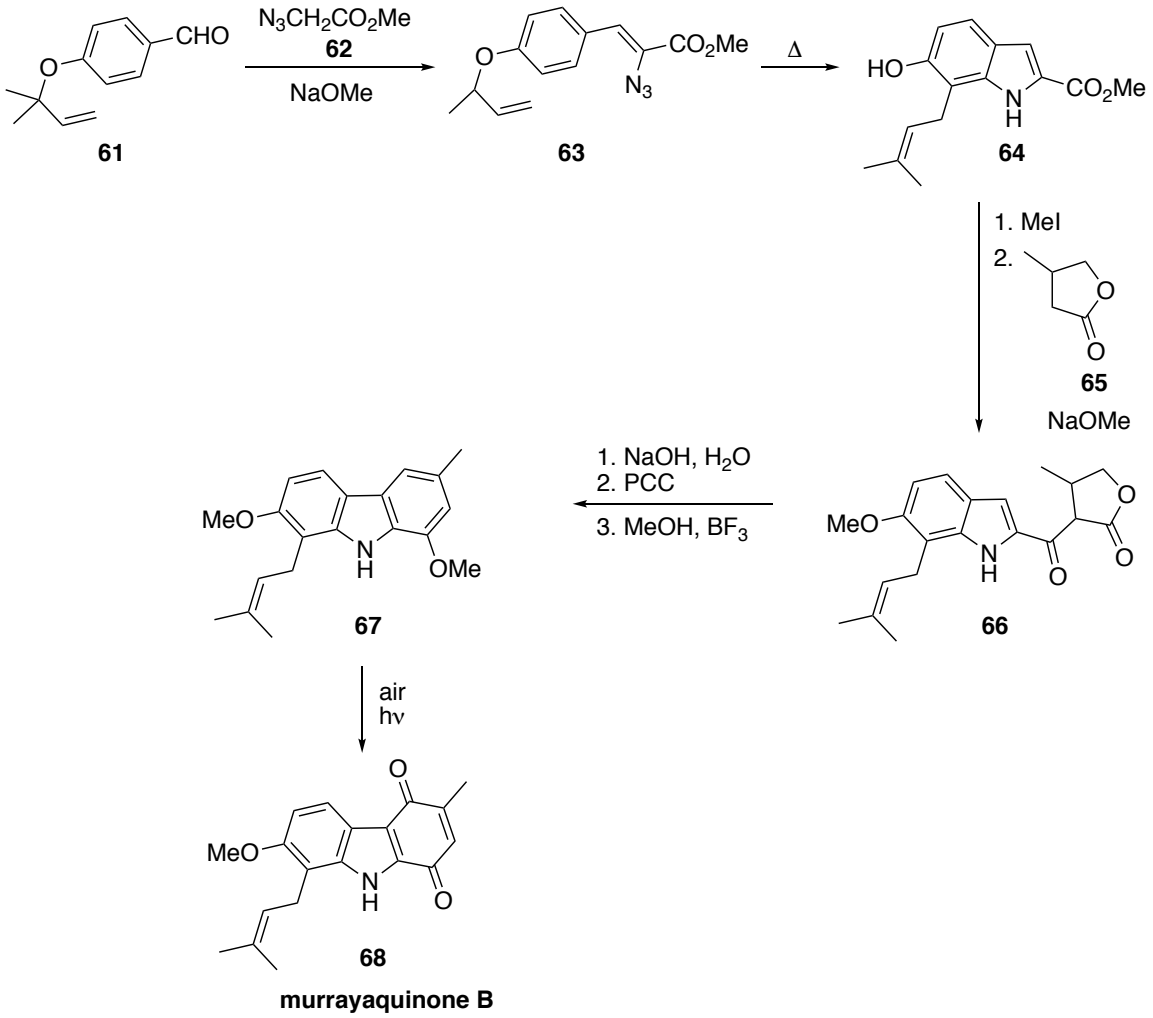


Scheme 9 Synthesis of unsymmetrical and fully substituted carbazoles via [2+2+2] cycloaddition pathway

1.3.2.2 Carbazole Synthesis via Indole-2-carboxylate Intermediate

Moody and co-workers synthesised murrayaquinone B (**68**) via an indole-2-carboxylate intermediate **64** (**Scheme 10**).[21] The benzaldehyde **61** was treated with methyl azidoacetate **62** in the presence of sodium methoxide to give compound **63**. This step was followed by thermally-induced cyclisation and Claisen rearrangement reactions to give compound **64**. Subsequent methylation and condensation with 4-methylbutyrolacetone (**65**) resulted in the formation of compound **66**. Heating in aqueous dioxane in the presence of NaOH facilitated lactone hydrolysis to the corresponding alcohol and concomitant decarboxylation. Pyridinium chlorochromate (PCC) oxidation to the

aldehyde followed by cyclization in the presence of BF_3 afforded carbazole **67**, which was readily converted to murrayaquinone B (**68**).

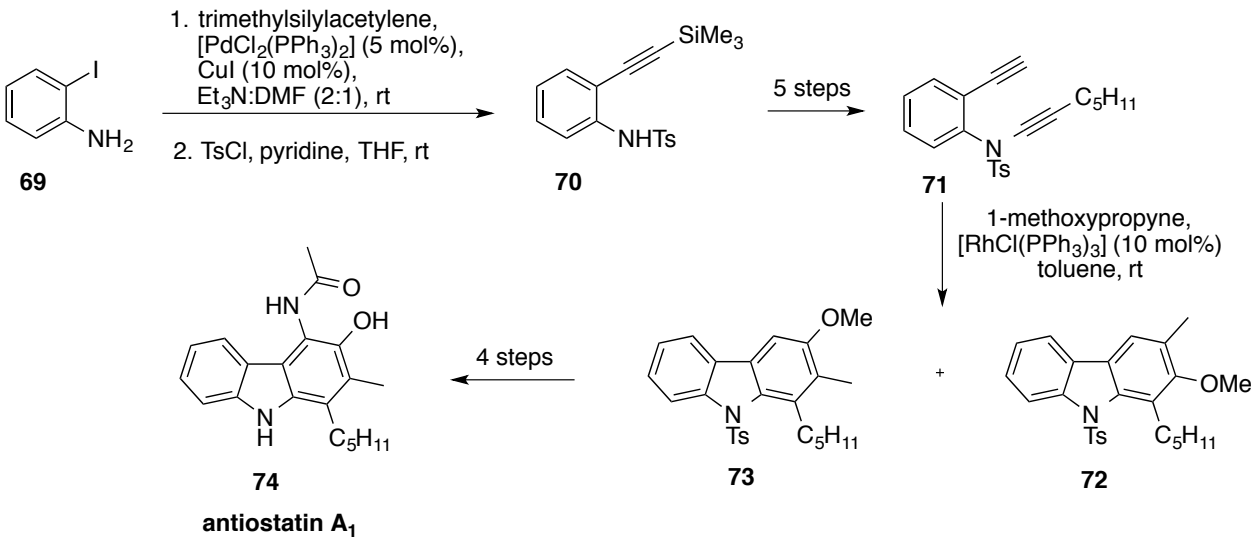


Scheme 10 Synthesis of murrayaquinone B via indole-2-carboxylate intermediate **(64)**

1.3.2.3 Rhodium-catalysed Cycloadditions of Alkyne Derivatives: Vollhardt-type Cyclisation

Witulski and co-workers utilised a sequence involving a Sonogashira cross-coupling, a chemo- and regioselective rhodium-catalysed cross alkyne cyclotrimerisation and palladium-catalysed arylamidation reactions as key steps in the first total synthesis of the carbazole-containing natural product antiostatin A_1 (**74**) (**Scheme 11**).[22-23]

Specifically, the Sonogashira reaction of *o*-iodoaniline (**69**) with trimethylsilylacetylene followed by tosylation of the aniline nitrogen gave the anilide **70** that itself was converted into the diyne **71** in five steps. The critical [2+2+2] cyclotrimerisation reaction of diyne **71** with 1-methoxypropyne could be achieved using 10 mol % of Wilkinson's catalyst [$RhCl(PPh_3)_3$] in toluene at room temperature to give the carbazole **73** as the major product as well as the regioisomer **72**. The desired isomer **73** was converted to the natural product, antiostatin A_1 (**74**) over four additional steps.



Scheme 11 First total synthesis of antiostatin A_1 by Rhodium-catalysed crossed [2+2+2] cycloadditions

1.3.3. The Formation of the Central Pyrrole (B) Ring from Biphenyl Derivatives.

The final class of carbazole synthesis is the formation of the pyrrole ring (B) from biphenyl derivatives (**Figure 4**). This process can occur either by C–N bond formation from biphenyl derivative **75** or C–C bond formation with **76** to form the carbazole (**1**).

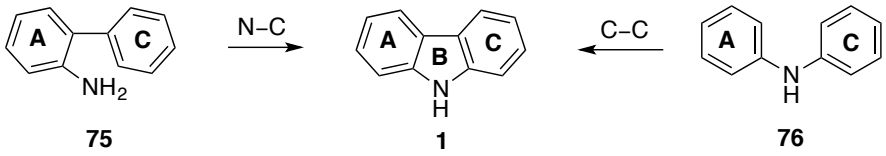
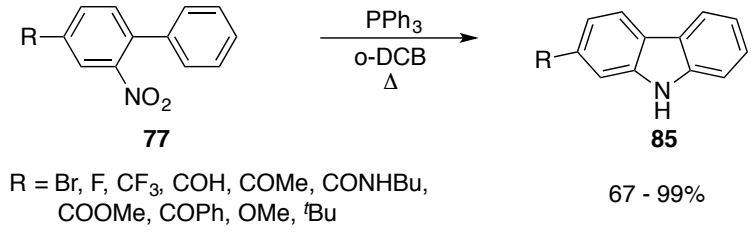


Figure 4 Formation of pyrrole (B) ring from biphenyl derivatives

1.3.3.1 Cadogan Cyclisation

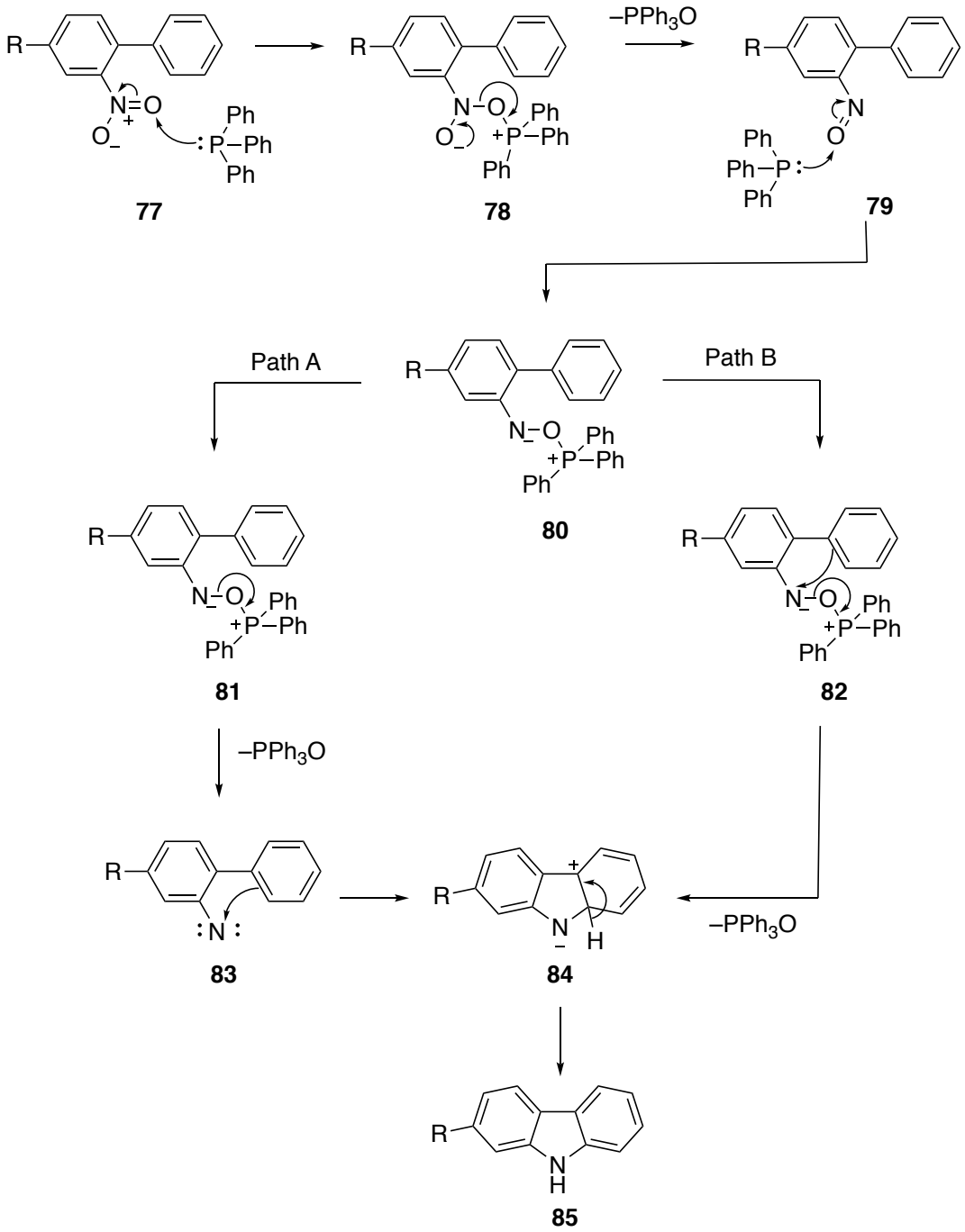
A common method for carbazole synthesis involves the reductive cyclisation of 2-nitrobiphenyl derivatives in the presence of organophosphorus reagents, also known as the Cadogan cyclisation.[24] Subjecting a range of 2-nitrobiphenyls to PPh_3 in refluxing orthodichlorobenzene (*o*-DCB) gave the desired carbazoles in good yield. (**Scheme 12**)



Scheme 12 Cadogan cyclisation reaction to afford the carbazole framework

Scheme 13 shows the proposed mechanism for Cadogan cyclisation to carbazoles (**85**). Reductive deoxygenation via nucleophilic attack of PPh_3 onto the nitro group gives compound (**80**), which is postulated to proceed via two alternate pathways to afford the carbazole. Path A involves first elimination of PPh_3O followed by nitrene insertion and after elimination of H^+, gives the desired carbazole (**85**). In path B, compound (**80**)

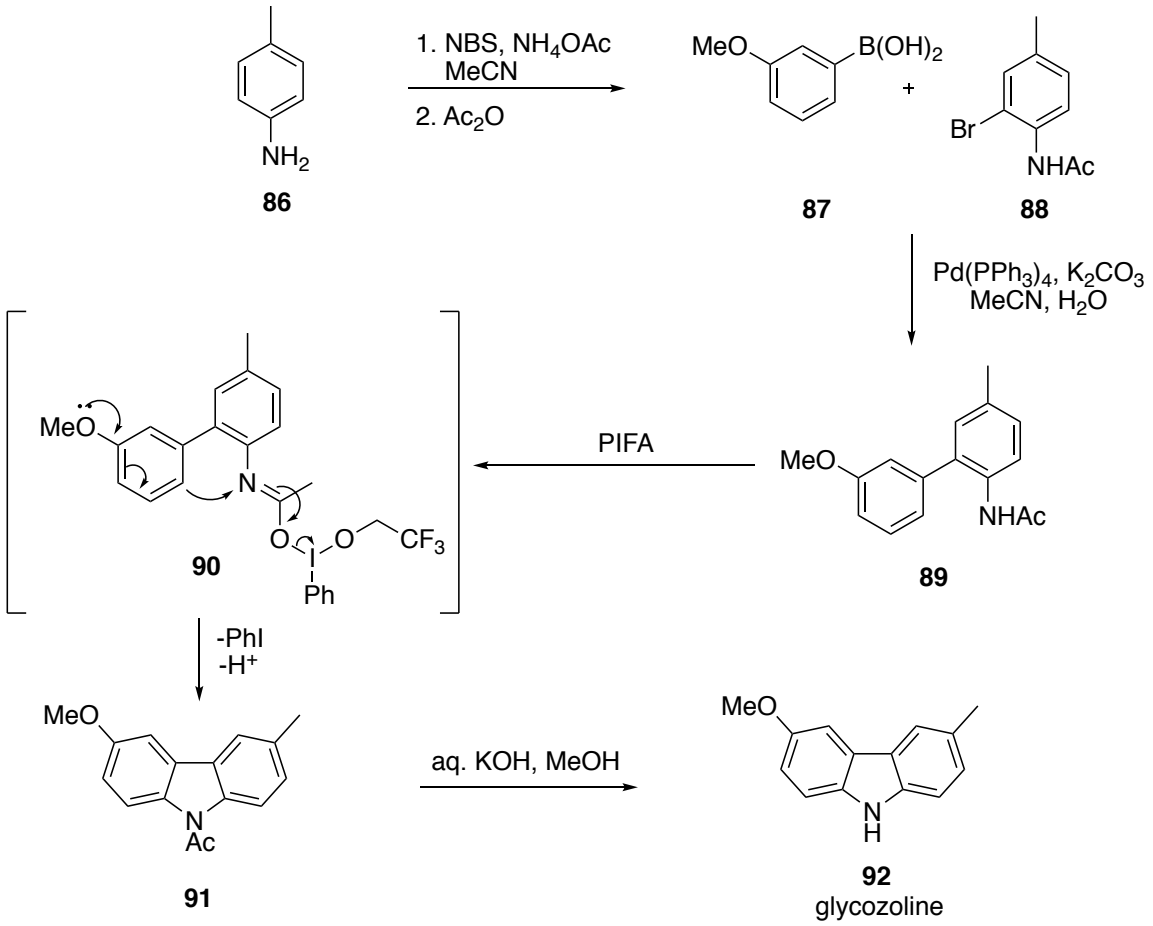
undergoes an initial cyclisation with elimination of PPh_3O followed by H^+ elimination, giving the desired carbazole (**85**).



Scheme 13 Proposed mechanism for Cadogan cyclisation to carbazoles

1.3.3.2 Hypervalent Iodine (III) Mediated Carbazole Synthesis

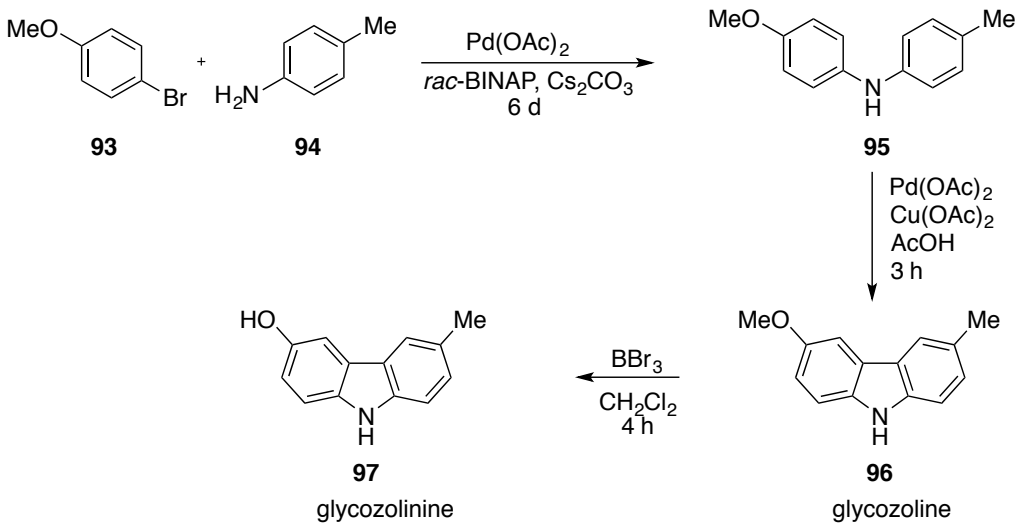
Kajiyama and co-workers synthesised glycozoline (**92**) (**Scheme 14**) through an oxidative cyclisation using an electrochemically generated hypervalent iodine oxidant.[25] The Suzuki-Miyaura coupling of the boronic acid **87** with acetanilide **88** gave diaryl **89**. The key oxidative cyclisation of compound **89** using oxidant $PhI(OCH_2CF_3)_2$ (PIFA) proceeded under basic conditions via cyclisation of intermediate **90** to give the *N*-acetyl protected carbazole **91**. Subsequent treatment with KOH/MeOH removed the acetyl group to give the target carbazole, glycozoline (**92**).



Scheme 14 Synthesis of glycozoline via hypervalent iodine (III) mediated oxidative cyclisation

1.3.3.3 Palladium(II)-catalysed Carbazole Synthesis

Knölker and co-workers have extensively explored Pd-catalysed oxidative cyclisation of biarylamines to form the carbazole motif.[26] The reaction sequence involves Pd[0]-catalysed Buchwald-Hartwig amination of *p*-bromoanisole (**93**) and *p*-toluidine (**94**) and subsequent palladium[II]-catalysed oxidation cyclisation of the resulting product **95** to give 6-oxygenated carbazole alkaloids **96**/**97** as shown in **Scheme 15**. Deprotection of glycozoline (**96**) with boron tribromide gave glycozolinine (**97**). Glycozolinine (**97**) was further elaborated into other natural products through a series of manipulations.



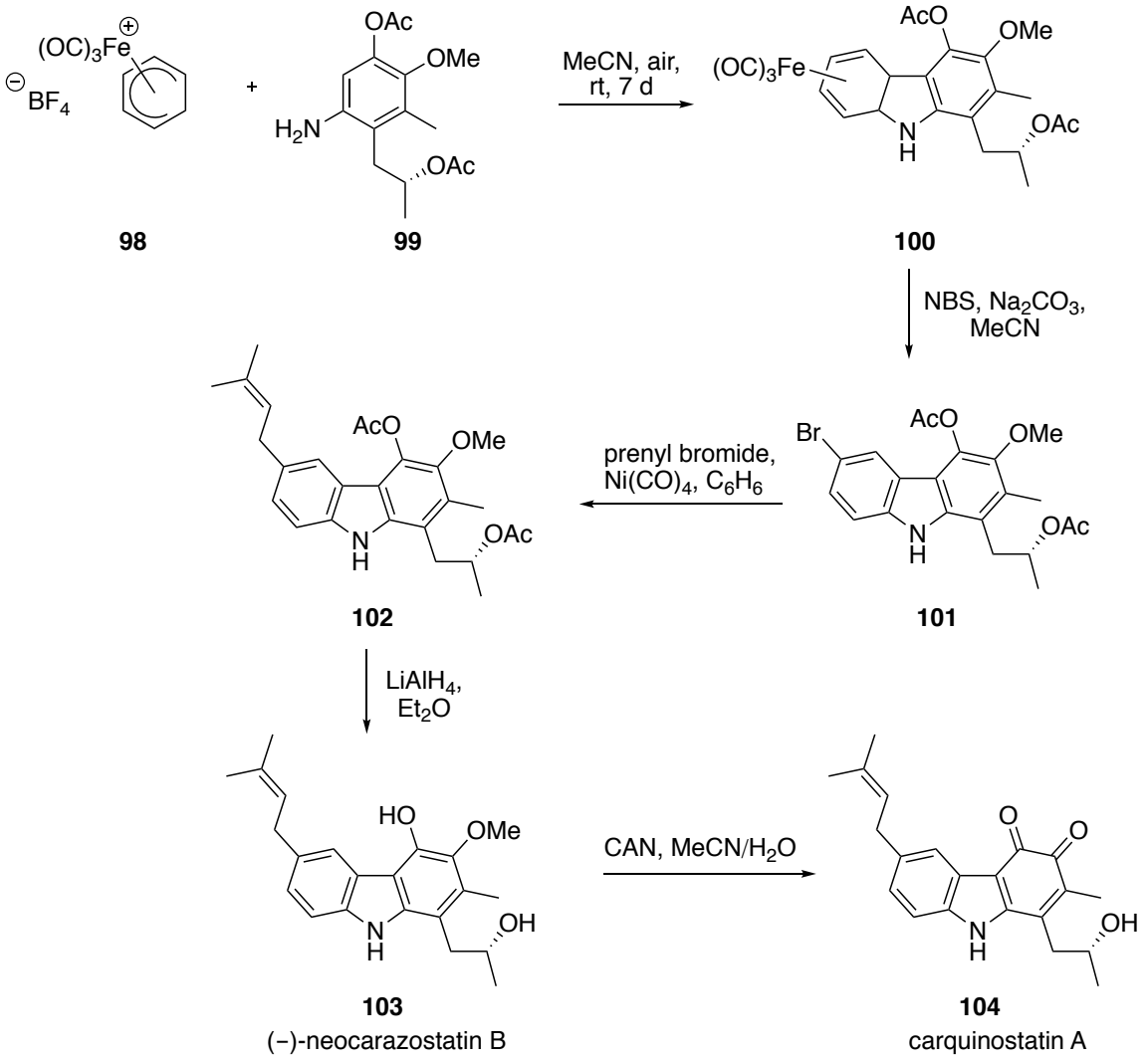
Scheme 15 Oxidative cyclisation of biarylamines to carbazoles; synthesis of glycozolinine and glycozoline

1.3.3.4. Iron-arene Complex-mediated Carbazole Synthesis

Knölker also pioneered a new route to carbazoles involving an arylation mediated by an iron-arene complex followed by intramolecular C–N bond formation.[27-28] The group reported the synthesis of (–)-neocarazostatin B (**103**) and carquinostatin A (**104**) via this iron-mediated oxidative cyclisation (**Scheme 16**).[29]

The reaction of the tetrafluoroborate salt of the iron-arene complex **98** and aryl amine **99** gave the tricarbonyliron–coordinated carbazole **100** in a single step. Aromatisation and

demetallation with NBS under basic conditions afforded the bromocarbazole **101**. Treatment of compound **101** with prenyl bromide and $Ni(CO)_4$ in benzene gave compound **102**. Removal of the acetate protecting groups with $LiAlH_4$ afforded (–)-neocarazostatin B (**103**), which could be converted into carquinostatin A (**104**) under oxidative conditions (ceric(IV) ammonium nitrate).

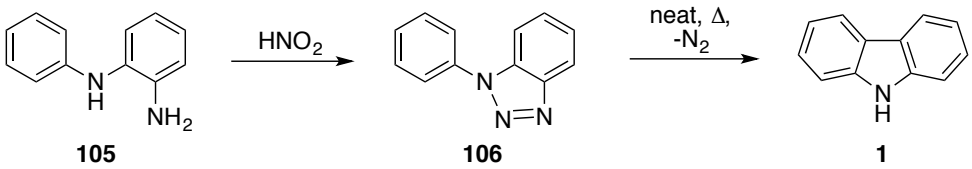


Scheme 16 Synthesis of (–)-neocarazostatin B and carquinostatin A via iron-arene mediated synthesis

1.3.3.5 Graebe-Ullmann Synthesis

The Graebe-Ullmann synthesis is the transformation of 1-phenylbenzotriazole (**106**) to a carbazole (**1**) under thermal reaction conditions.[30] The benzotriazole can be prepared by

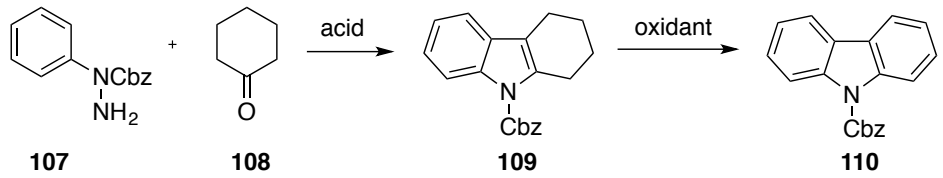
diazotisation of *N*-(2-aminophenyl)aniline (**105**) and under thermal conditions gives the resulting carbazole (**1**) (**Scheme 17**). Little is known about the reaction mechanism but this transformation is thought to proceed via a diradical intermediate generated in the thermolysis of the triazole.



Scheme 17 Graebe-Ullmann synthesis of carbazoles

1.3.3.6 Fischer Indolisation

A common method of preparing carbazoles utilises the Fischer indole synthesis of 1,2,3,4-tetrahydrocarbazole and subsequent aromatisation. The Fischer indolisation (or Fischer-Borsche synthesis, Borsche-Dreschel reaction) is a classical illustration of indole synthesis and a common method of synthesising carbazoles.[31-32] Fischer indolisation of Cbz-protected aryl hydrazines **107** with cyclohexanone (**108**) in acidic conditions gives the annulated indole/1,2,3,4-tetrahydrocarbazole **109** (**Scheme 18**).[33] Following condensation of the hydrazine and ketone to afford an ene-hydrazine, this reaction involves protonation, formation of a new C-C bond via a [3,3]-sigmatropic rearrangement and elimination of ammonia. Borsche was the first to realise the scope of the Fischer indole synthesis and demonstrate its use to prepare a wide range of tetrahydrocarbazoles.[34] Both organic and inorganic acids such as sulfuric and acetic acid have been employed, although acetic acid provided products in superior purities. Oxidative aromatisation of 1,2,3,4-tetrahydrocarbazole **109** with an oxidant such as DDQ in benzene gave the corresponding carbazole **110**. Other oxidants such as lead oxide, mercury acetate, palladium chloride, chloranil or Pd/C have also been employed.



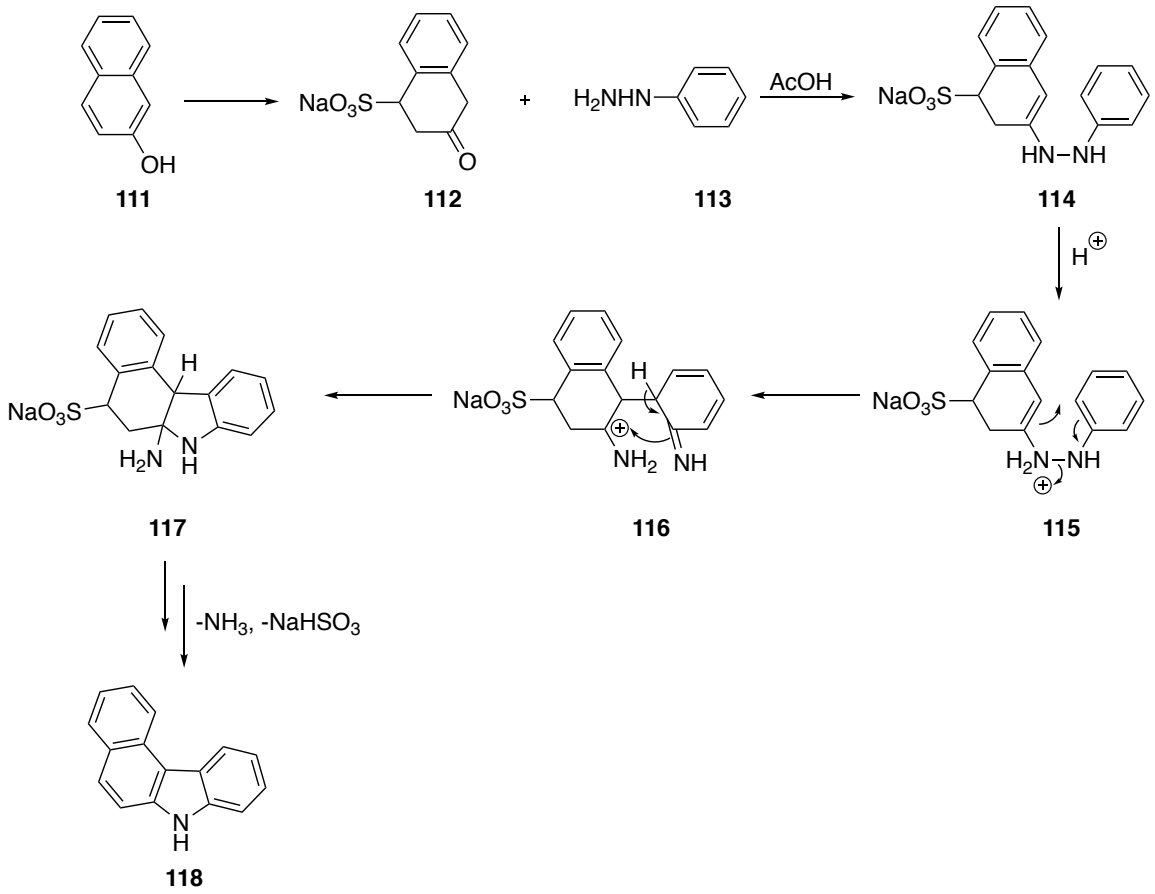
107 **108** **109** **110**

Scheme 18 Fischer indole route to carbazoles

1.3.3.7 Bucherer Carbazole Synthesis

The Bucherer carbazole synthesis is the reaction of α-naphthols **111** (or α-naphthylamines) with phenylhydrazine (**113**) and leads to the formation of 3,4-benzocarbazoles (**118**) (**Scheme 19**).[35]

The reaction of 3-tetralone-1-sulfonate (**112**) with phenylhydrazine (**113**) as a nucleophile in 40 % acetic acid at room temperature afforded the phenylhydrazinium 1,2-dihydro-3,4-benzocarbazole-2-sulfonate (**117**) via a series of protonation steps. Subsequent loss of ammonia and $NaHSO_3$ gave the desired 3,4-benzocarbazole (**118**).

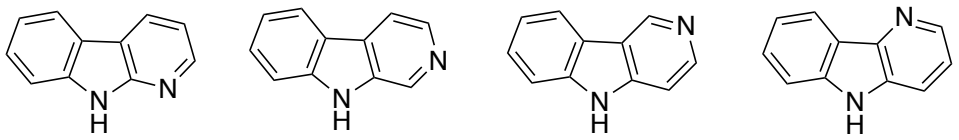


Scheme 19 Bucherer carbazole synthesis to 3,4-benzocarbazoles

In principle, the Bucherer carbazole synthesis, the Fischer indole synthesis and Borsche-Drechsel carbazole synthesis from phenylhydrazines and cyclic ketones all proceed in a similar fashion.

1.4 Carbolines (α-, β-, γ-, δ-)

Pyrido[*b*]indoles are known as carbolines. Carbolines consist of a tricyclic moiety structurally related to both indole and carbazole compounds and depending on the way in which the rings are fused, they are designated as α-, β-, γ-, δ-, respectively (**Figure 5**).[36]



119 α−carboline | **120** β−carboline | **121** γ−carboline | **122** δ−carboline

Figure 5 Isomers of Carbolines

The α-carboline structure (pyrido[2,3-b]indole) (**119**) forms the core structure of a number of natural products.[37] While not as common in nature as β-, γ- carbolines, interest in the synthesis of natural and synthetic α-carbolines has arisen due to their cytotoxicity, anticancer and CNS activity.[36]

β-Carboline alkaloids (**120**) are widespread in plants and animals, and frequently act as benzodiazepine inverse agonists. As components of the liana *Banisteriopsis caapi,* the β-carbolines harmine, harmaline, and tetrahydroharmine play a pivotal role in the pharmacology of the indigenous psychedelic drug ayahuasca.[38] These compounds prevent the breakdown of dimethyltryptamine in the gut by reversibly inhibiting monoamine oxidase, thus making them psychoactive upon oral administration. Some β-carbolines, notably tryptoline and pinoline, may be formed naturally in the human body. The importance of β-carbolines demands efficient synthetic methodologies.

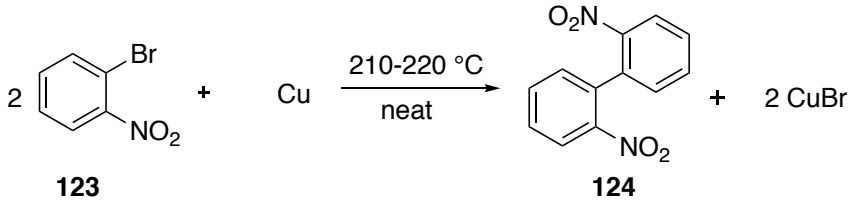
γ-Carbolines (**121**) are less studied than their β-carboline analogues **120**, however, the biological properties of γ-carboline (**121**) are equally important as their β-counterparts (**120**). Compounds containing γ-carbolines (**121**) have attracted interest due to their ability to inhibit the activity of monoamine oxidase (MAO) and to influence the effects of important neurotransmitters such as histamine and serotonin.[39]

The carboline core is usually built from a suitable functionalised indole such as a tryptamine derivative, onto which the fused pyridine ring is introduced. Indoles, which are activated substrates, efficiently undergo intramolecular Friedel-Crafts-type reactions such as Pictet-Spengler (PS) and the Bischler-Napieralski (BN) reactions. Methodologies based on transition metal catalysed cyclisation for the synthesis of the pyrrole ring have also emerged in recent times.[40] Subsequent functionalisation *en route* to natural products or synthetic drug candidates may be necessary.

1.5 Key reactions utilised in this Thesis

1.5.1 The Ullmann Reaction

The Ullmann reaction is a classic C–C bond forming process.[41] The original form of this reaction was reported in 1901 and involved the homo-coupling of two equivalents of an aryl halide **123** in the presence of copper powder at high temperature to give the corresponding symmetrical biaryl **124** (**Scheme 20**).[42]



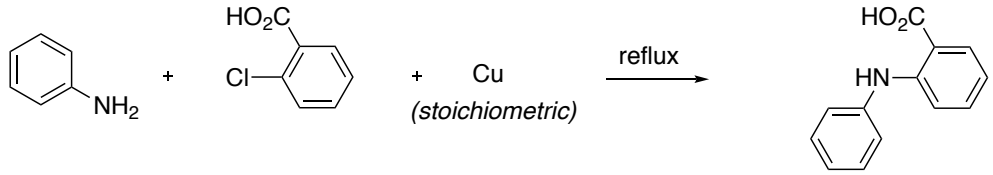
Scheme 20 Original Ullmann Reaction

Since the discovery of the Ullmann reaction, its general scope and limitations have been established. These are summarised below and in **Scheme 21**.[41] Evano, Blanchard and Toumi provide an in-depth review of the topic.[41]

- Both halogenated aromatic and heteroaromatic compounds can participate in the reaction;
- Aryl iodides are more reactive than their bromide counterparts, which are more reactive than the corresponding aryl chlorides.
- Substituents can affect the reactivity. Electron-withdrawing groups (especially NO_2, –COOR, –CHO) located in the *ortho*-position relative to the halogen can facilitate the coupling process. Conversely, bulky groups can have a detrimental effect, while electron-donating groups anywhere on either ring generally diminish the yields and decrease the rate of cross-coupling.
- Copper powder with freshly cleaned metal surfaces is normally used.
- DMF is the most common solvent used, although pyridine, quinolone, nitrobenzene, DMSO and *p*–nitrotoluene have also been employed.
- Long reaction times and temperatures in excess of 200 °C are often required to achieve reasonable reaction rates.

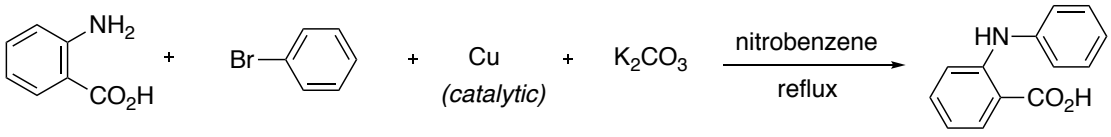
- In cross-coupling reactions, the corresponding homo-coupling products are commonly encountered by-products.
- Further developments of the Ullmann reaction extend beyond C–C bond formation to the synthesis of diarylamines, diarylethers and arylamides. Examples of this are shown in Scheme 21. Carbon–heteroatom bond formations can often be competing reactions if the substrate contains acidic hydrogens (–OH, –COOH, $–NH_2$, $–SO_2NH_2$).

Ullmann Condensation Reaction: Synthesis of Diarylamines



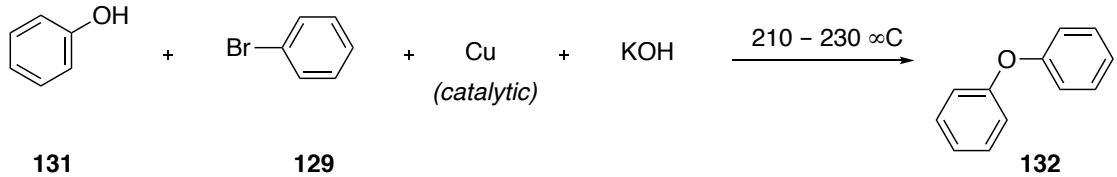
125 **126** **127**

Goldberg



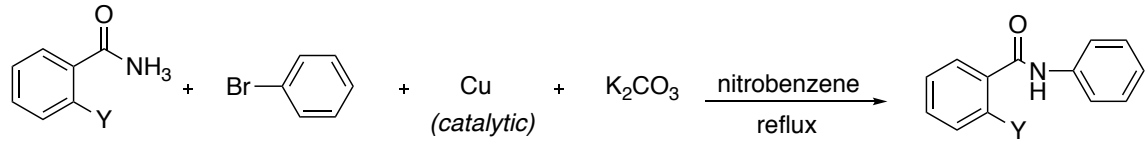
128 **129** **130**

Ullmann Condensation Reaction: Synthesis of Diarylethers



131 **129** **132**

Goldberg Condensation Reaction: Synthesis of Arylamides



133 **129** **134**

Y = H, OH Y= H, OH

Scheme 21 Variations of Ullmann reaction: Synthesis of diarylamines, diarylethers and arylamides

1.5.2 The Palladium[0]-catalysed Ullmann Cross-coupling Reaction

The Pd[0]-catalysed variant of the Ullmann cross-coupling reaction was first reported in 1993 by Shimizu and co-workers and used aryl bromide **123**, iodopyridine **135**, four equivalents of copper powder and 5 mol % of $Pd(PPh_3)_4$ as a catalyst to form (2-nitrophenyl)pyridine **136** (**Scheme 22**).[43]

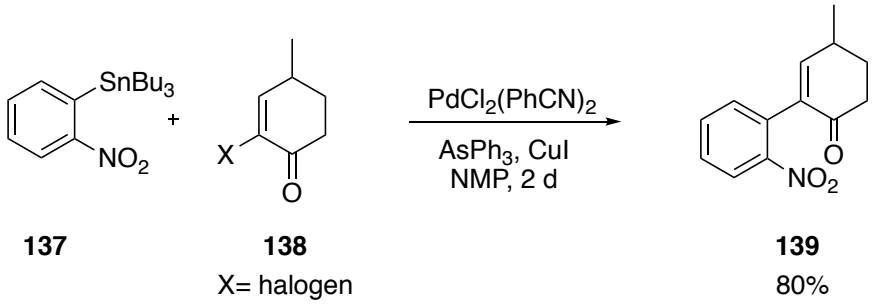
135 **123** **136** 90%

Scheme 22 First example of a Pd[0]-catalysed Ullmann cross-coupling reaction

Shimizu and co-workers reported a wide range of Pd catalysts including $Pd(PPh_3)_4$, $PdCl_2$, and $PdCl_2(PPh_3)_2$. The most notable outcome from the study was that the cross-coupling reactions could be conducted under relatively mild conditions and homo-coupling was not observed.

1.5.3 The Pd[0]-catalysed Ullmann Cross-coupling Route to Indoles

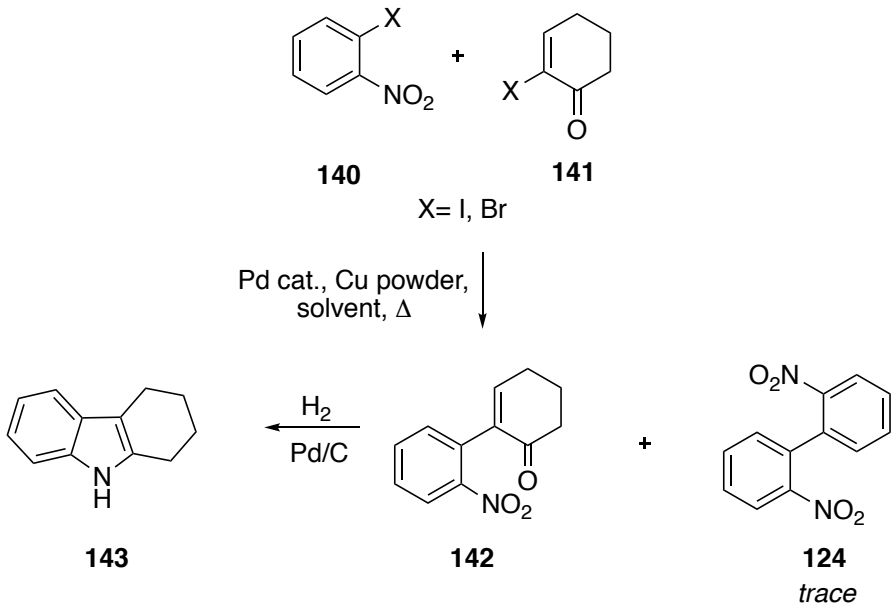
The Pd[0]-catalysed Ullmann cross-coupling has provided a useful route to indoles. Typically, this important heterocyclic ring system is obtained by using the Fischer indole synthesis as described previously. The limitations of this approach include the harsh conditions required to perform the [3,3]–sigmatropic rearrangement of the intermediate ene-hydrazine and lack of regiocontrol when using ketones with more than one enolisable proton. However, Scott and Soderberg (**Scheme 23**) have reported the use of a Stille coupling with aryl tin compound **137** and cyclic enone **138** to produce compound **139**, a precursor to carbazoles.[44] This process allows for complete regiocontrol in the formation of the C–C bond which has provided important background to the work in this thesis.



Scheme 23 Scott and Soderberg Stille Coupling of tributyl(2-nitrophenyl)stannane and α-halocyclohexenone

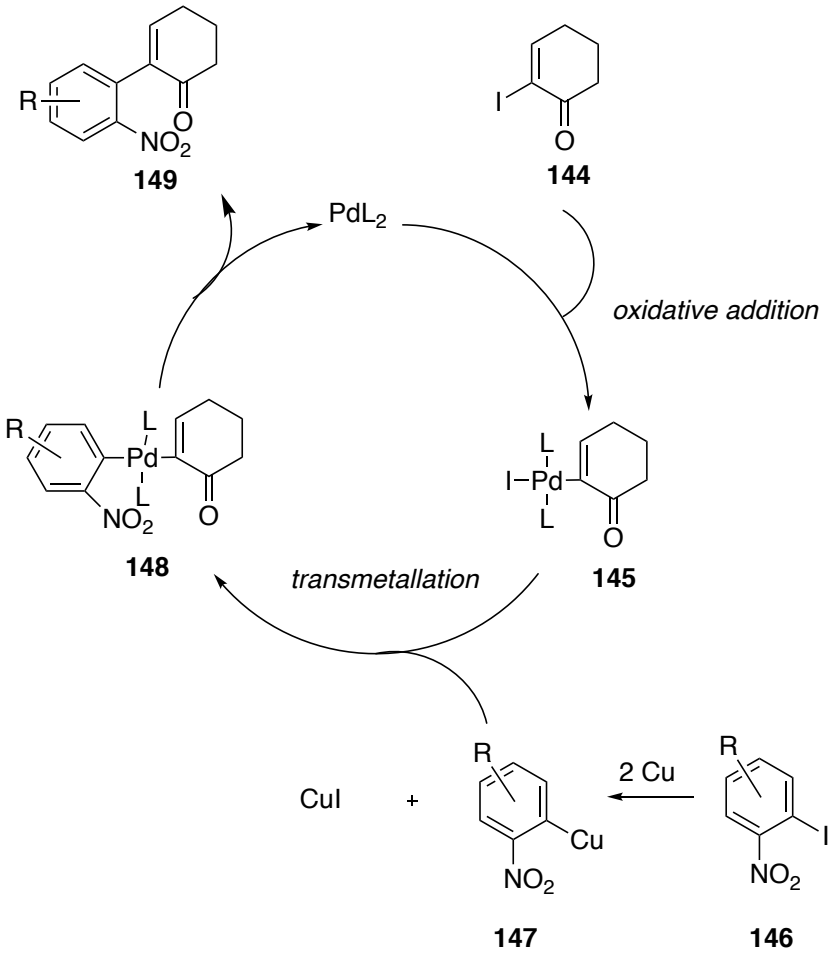
A recent Pd[0]-catalysed Ullmann cross-coupling approach by Banwell and co-workers addresses the regiochemical issues associated with the Fischer indole synthesis while also avoiding the use of stannanes.[45] The method involves a simple two-step protocol from readily available starting materials and reagents. As with other Ullmann cross-coupling methods, the reaction is performed directly between two halogenated substrates; Suzuki, Negishi, Stille and Kumada protocols differ as they typically involve cross-coupling between a preformed metallated species.

Banwell and coworkers' two-step protocol to annulated indoles, shown in **Scheme 24**, proceeds first with a Pd[0]-catalysed Ullmann cross-coupling reaction, followed by a reductive cyclisation to form tetrahydrocarbazole **143**.[45]



Scheme 24 Pd[0]-catalysed Ullmann Cross-coupling reaction to Indoles

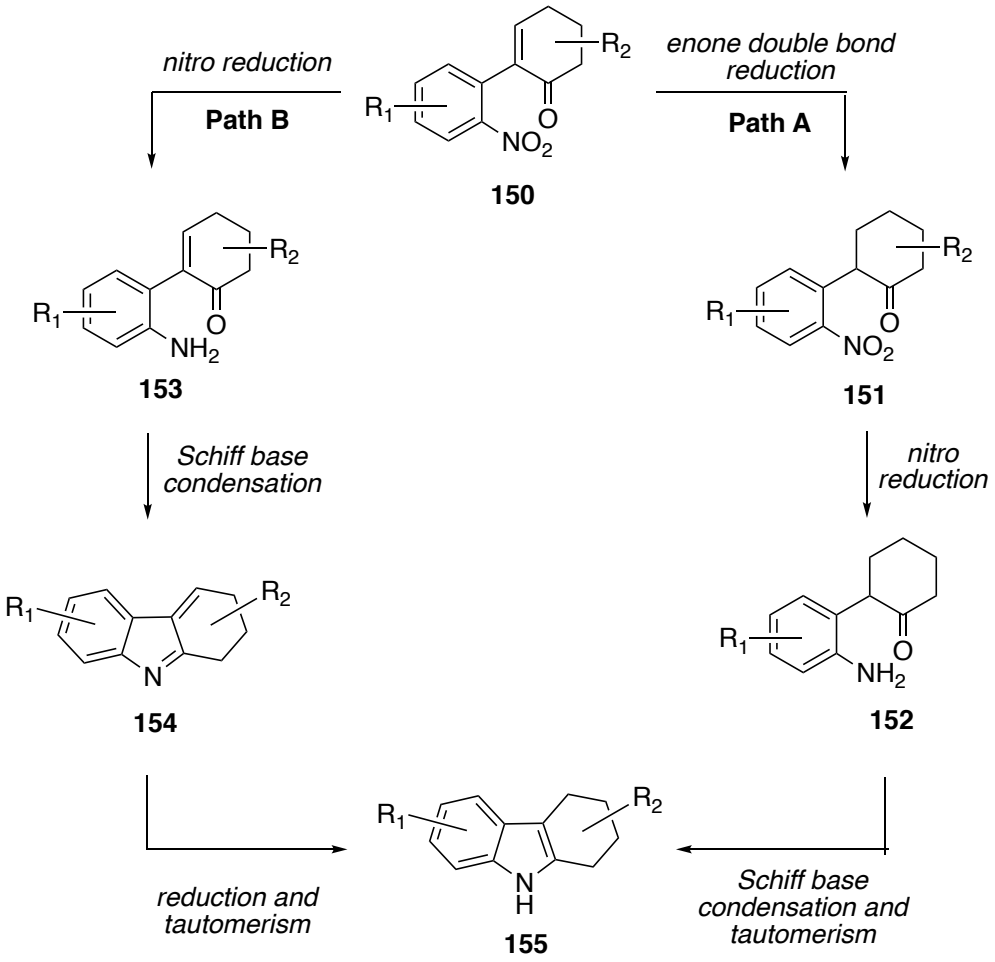
Based on a postulated catalytic cycle by Shimizu, **Scheme 25** depicts the proposed mechanism of the Pd[0]–catalysed Ullmann cross-coupling reaction. It is presumed that the aryl halide **146** is selectively metallated with copper[0] to give the copper derivative **147** while the cyclic enone **144** undergoes oxidative addition with palladium[0] to give the palladium intermediate **145**. Transmetallation affords the palladium[II] species **148**, which undergoes a reductive elimination to give the desired cross-coupled product **149**.



Scheme 25 Catalytic cycle proposed for the Pd[0]-catalysed cross-coupling of α-iodocyclohexenone and 2-iodonitrobenzene derivatives

The Pd[0]-catalysed Ullmann cross-coupling product was subjected to reaction with hydrogen in the presence of palladium on carbon to generate the target indole. It is speculated that indole formation can occur through one of two pathways or a combination of the two. One pathway (**Scheme 26**, Path A) involves initial reduction of the enone double bond of compound **150** to give compound **151**. The resulting intermediate **151** then undergoes reduction of the nitro moiety to give the aniline **152** which engages in an intramolecular Schiff base condensation reaction. This is followed

by tautomerisation of the initially formed isoindole to give its aromatic counterpart **155**. The second pathway (**Scheme 26**, Path B) begins with the reduction of the aromatic nitro moiety of compound **150** to the corresponding aniline **153**. The latter can then undergo an intramolecular Schiff base condensation reaction to give isoindole **164**. At this point the carbon–carbon double bond is reduced and, following tautomerisation, the annulated indole **155** is formed. There is literature evidence to support path A, where a compound was isolated where reduction of the double bond has occurred but the nitro moiety was left untouched.



Scheme 26 Possible pathways associated with the reductive cyclisation of the cross-coupling product **150** to give annulated indole **155**.

1.5 Key reactions utilised in this Thesis

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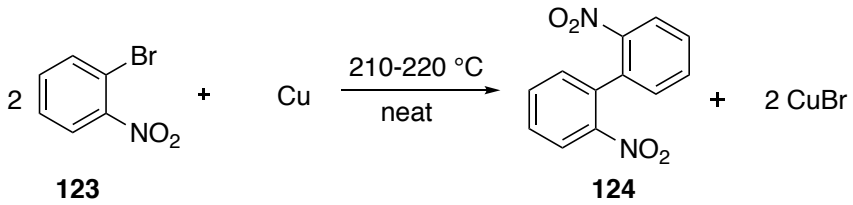

Scheme 27 Original Ullmann Reaction

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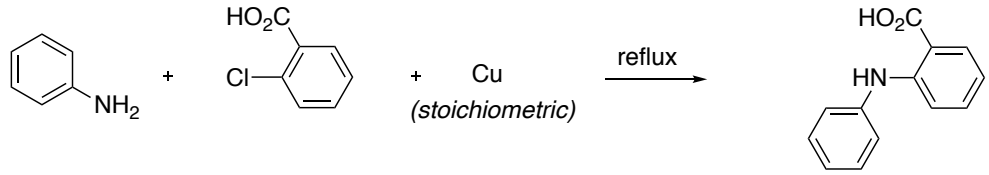
- Both halogenated aromatic and heteroaromatic compounds can participate in the reaction;
- Aryl iodides are more reactive than their bromide counterparts, which are more reactive than the corresponding aryl chlorides.
- Substituents can affect the reactivity. Electron-withdrawing groups (especially NO_2, –COOR, –CHO) located in the *ortho*-position relative to the halogen can facilitate the coupling process. Conversely, bulky groups can have a detrimental effect, while electron-donating groups anywhere on either ring generally diminish the yields and decrease the rate of cross-coupling.
- Copper powder with freshly cleaned metal surfaces is normally used.
- DMF is the most common solvent used, although pyridine, quinolone, nitrobenzene, DMSO and *p*–nitrotoluene have also been employed.
- Long reaction times and temperatures in excess of 200 °C are often required to achieve reasonable reaction rates.

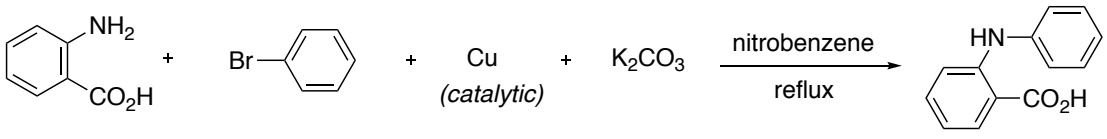
- In cross-coupling reactions, the corresponding homo-coupling products are commonly encountered by-products.
- Further developments of the Ullmann reaction extend beyond C–C bond formation to the synthesis of diarylamines, diarylethers and arylamides. Examples of this are shown in Scheme 21. Carbon–heteroatom bond formations can often be competing reactions if the substrate contains acidic hydrogens (–OH, –COOH, $–NH_2$, $–SO_2NH_2$).

Ullmann Condensation Reaction: Synthesis of Diarylamines



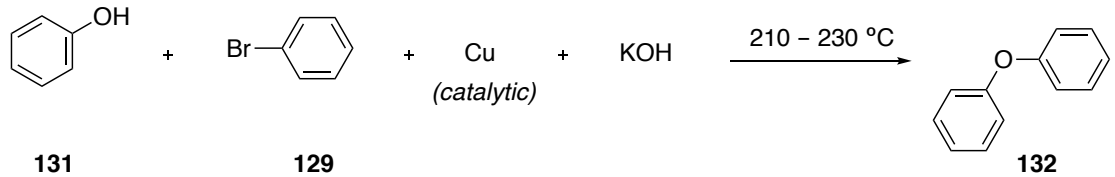
125 **126** **127**

Goldberg



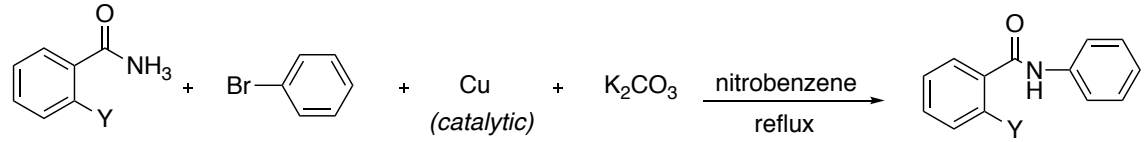
128 **129** **130**

Ullmann Condensation Reaction: Synthesis of Diarylethers



131 **129** **132**

Goldberg Condensation Reaction: Synthesis of Arylamides



133 **129** **134**

Y = H, OH Y= H, OH

Scheme 28 Variations of Ullmann reaction: Synthesis of diarylamines, diarylethers and arylamides

1.5.2 The Palladium[0]-catalysed Ullmann Cross-coupling Reaction

The Pd[0]-catalysed variant of the Ullmann cross-coupling reaction was first reported in 1993 by Shimizu and co-workers and used aryl bromide **123**, iodopyridine **135**, four equivalents of copper powder and 5 mol % of $Pd(PPh_3)_4$ as a catalyst to form (2-nitrophenyl)pyridine **136** (**Scheme 22**).[43]

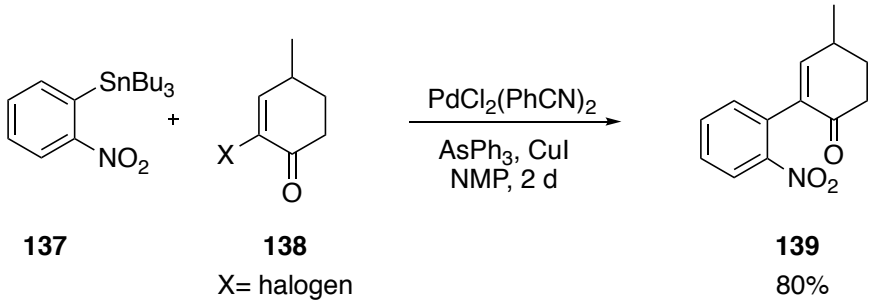
135 **123** **136** 90%

Scheme 29 First example of a Pd[0]-catalysed Ullmann cross-coupling reaction

Shimizu and co-workers reported a wide range of Pd catalysts including $Pd(PPh_3)_4$, $PdCl_2$, and $PdCl_2(PPh_3)_2$. The most notable outcome from the study was that the cross-coupling reactions could be conducted under relatively mild conditions and homo-coupling was not observed.

1.5.3 The Pd[0]-catalysed Ullmann Cross-coupling Route to Indoles

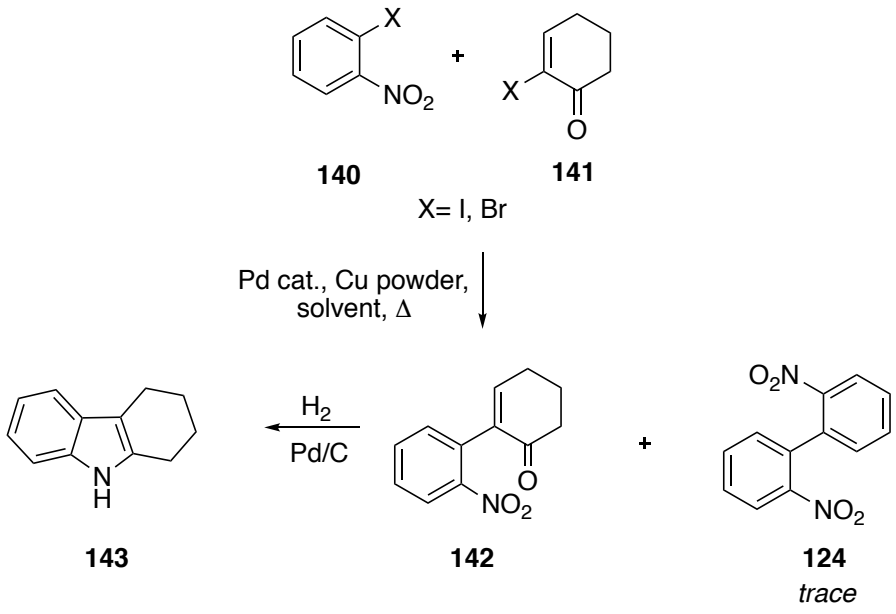
The Pd[0]-catalysed Ullmann cross-coupling has provided a useful route to indoles. Typically, this important heterocyclic ring system is obtained by using the Fischer indole synthesis as described previously. The limitations of this approach include the harsh conditions required to perform the [3,3]–sigmatropic rearrangement of the intermediate ene-hydrazine and lack of regiocontrol when using ketones with more than one enolisable proton. However, Scott and Soderberg (**Scheme 23**) have reported the use of a Stille coupling with aryl tin compound **137** and cyclic enone **138** to produce compound **139**, a precursor to carbazoles.[44] This process allows for complete regiocontrol in the formation of the C–C bond which has provided important background to the work in this thesis.



Scheme 30 Scott and Soderberg Stille Coupling of tributyl(2-nitrophenyl)stannane and α-halocyclohexenone

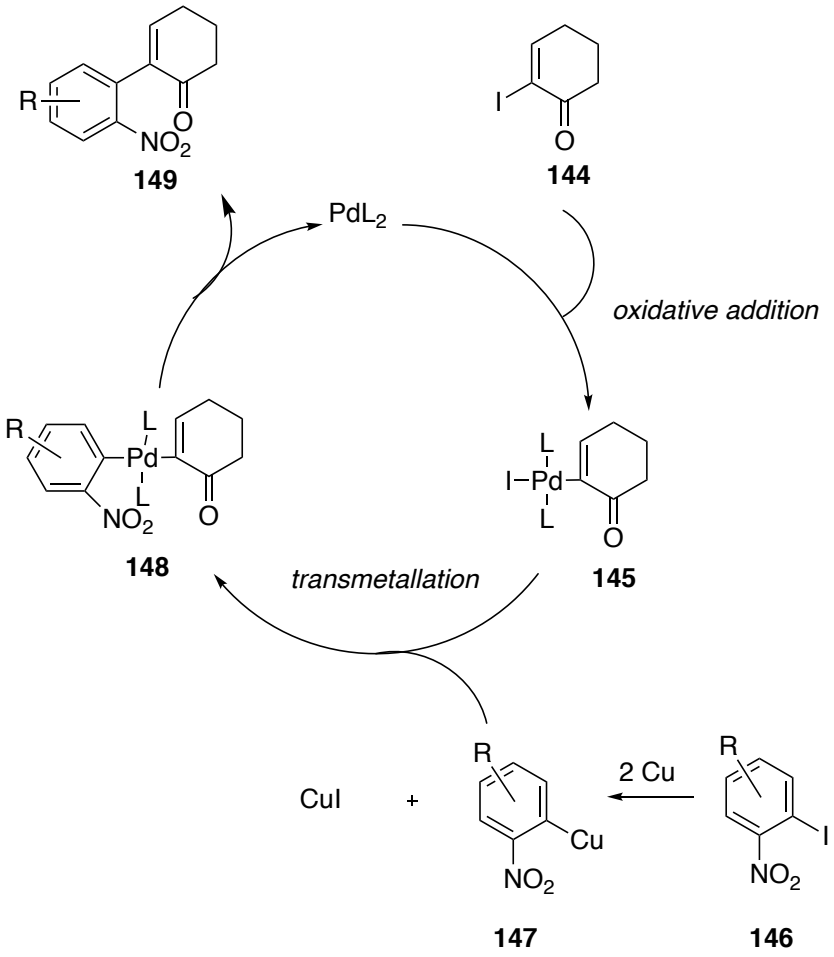
A recent Pd[0]-catalysed Ullmann cross-coupling approach by Banwell and co-workers addresses the regiochemical issues associated with the Fischer indole synthesis while also avoiding the use of stannanes.[45] The method involves a simple two-step protocol from readily available starting materials and reagents. As with other Ullmann cross-coupling methods, the reaction is performed directly between two halogenated substrates; Suzuki, Negishi, Stille and Kumada protocols differ as they typically involve cross-coupling between a preformed metallated species.

Banwell and coworkers' two-step protocol to annulated indoles, shown in **Scheme 24**, proceeds first with a Pd[0]-catalysed Ullmann cross-coupling reaction, followed by a reductive cyclisation to form tetrahydrocarbazole **143**.[45]



Scheme 31 Pd[0]-catalysed Ullmann Cross-coupling reaction to Indoles

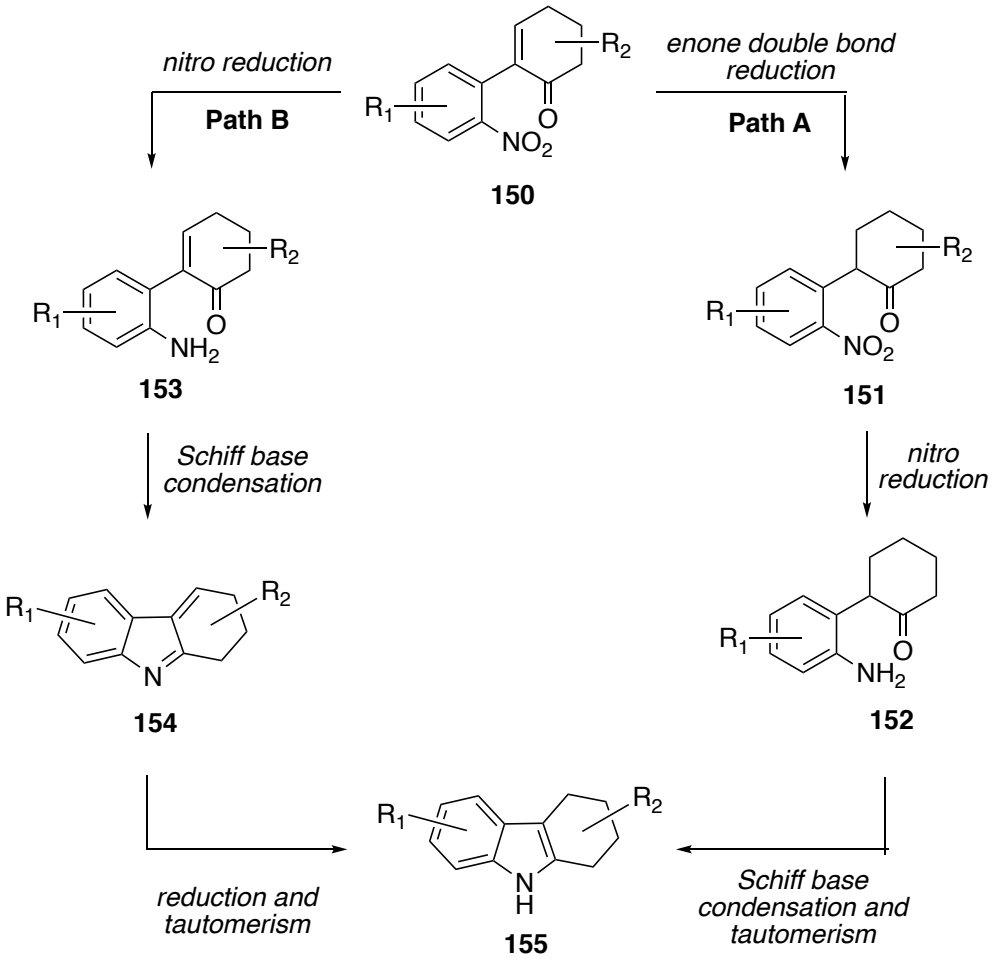
Based on a postulated catalytic cycle by Shimizu, **Scheme 25** depicts the proposed mechanism of the Pd[0]–catalysed Ullmann cross-coupling reaction. It is presumed that the aryl halide **146** is selectively metallated with copper[0] to give the copper derivative **147** while the cyclic enone **144** undergoes oxidative addition with palladium[0] to give the palladium intermediate **145**. Transmetallation affords the palladium[II] species **148**, which undergoes a reductive elimination to give the desired cross-coupled product **149**.



Scheme 32 Catalytic cycle proposed for the Pd[0]-catalysed cross-coupling of α-iodocyclohexenone and 2-iodonitrobenzene derivatives

The Pd[0]-catalysed Ullmann cross-coupling product was subjected to reaction with hydrogen in the presence of palladium on carbon to generate the target indole. It is speculated that indole formation can occur through one of two pathways or a combination of the two. One pathway (**Scheme 26**, Path A) involves initial reduction of the enone double bond of compound **150** to give compound **151**. The resulting intermediate **151** then undergoes reduction of the nitro moiety to give the aniline **152** which engages in an intramolecular Schiff base condensation reaction. This is followed

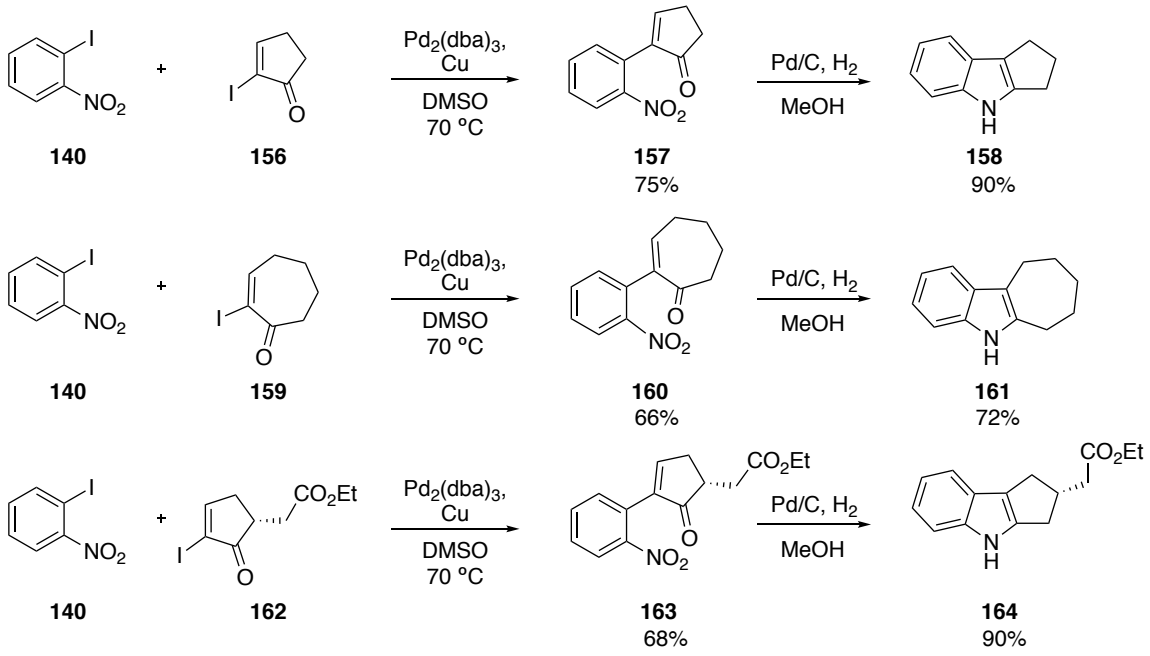
by tautomerisation of the initially formed isoindole to give its aromatic counterpart **155**. The second pathway (**Scheme 26**, Path B) begins with the reduction of the aromatic nitro moiety of compound **150** to the corresponding aniline **153**. The latter can then undergo an intramolecular Schiff base condensation reaction to give isoindole **164**. At this point the carbon–carbon double bond is reduced and, following tautomerisation, the annulated indole **155** is formed. There is literature evidence to support path A, where a compound was isolated where reduction of the double bond has occurred but the nitro moiety was left untouched.



Scheme 33 Possible pathways associated with the reductive cyclisation of the cross-coupling product **150** to give annulated indole **155**.

1.6 Prior contributions to Pd[0]-catalysed Ullmann Cross-coupling Reaction and Reductive Cyclisation: Indole and Natural Product synthesis

The Banwell group has used the Pd[0]-catalysed Ullmann cross-coupling protocol extensively.[45] Systematic trials indicated that a variety of palladium catalysts could be utilised; the combination of $Pd_2(dba)_3$, Cu[0] powder, iodinated versions of both coupling partners and DMSO as the solvent proved most effective. These conditions allowed the Ullmann cross-coupling reaction to proceed at temperatures around 50-70 °C (compared to prior approaches which proceeded at 200 °C). Minimal homo-coupling was observed under these conditions. A library of indoles, varying in the sizes of the appended ring structures, was generated in the two-step protocol in good yields (**Scheme 27**).[45]

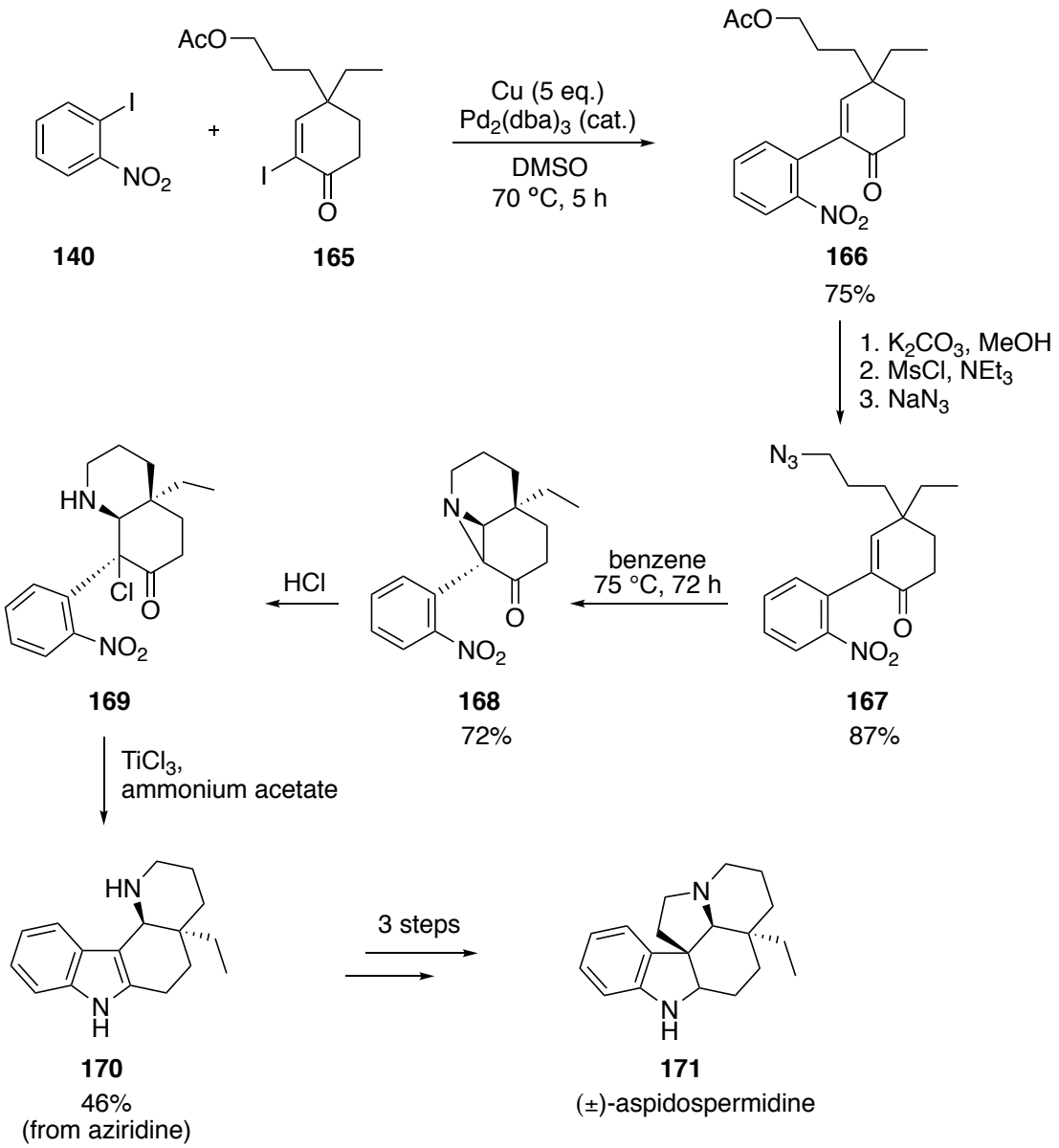


Scheme 34 Indole formation by Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation.

The Banwell group has successfully exploited the Pd[0]-catalysed Ullmann cross-coupling reaction in the synthesis of several natural products and details of each of these are presented in the following section.

1.6.1 Synthesis of (±)-apsidospermidine

The synthesis of the *apsidosperma* alkaloid (±)-apsidospermidine (**Scheme 28**, compound **171**) utilises the Pd[0]-catalysed Ullmann cross-coupling as one of the key steps.[46-47] The α-iodocylohexenone **165** was prepared in 11 steps from commercially available 3-ethoxycyclohexenone in a protocol described by Banwell and Lupton. Together with commercially available *o*-iodonitrobenzene **140**, the α-iodocyclohexenone **165** was subjected to a Pd[0]-catalysed Ullmann cross-coupling. This involved five equivalents of copper powder, catalytic $Pd_2(dba)_3$, and DMSO as the solvent at 70 °C. The cross-coupled product **166**, was hydrolysed to the alcohol, converted to the mesylate and reacted with sodium azide in DMF to give compound **167**. The resulting azide **167** engaged in a 1,3-dipolar cycloaddition after heating in benzene for three days to form, via an intermediate triazoline, aziridine **168**. The regioselective cleavage of the aziridine **168** was achieved by treatment with HCl in CH_2Cl_2 and the resulting hydrochloride salt of the α-chloroketone **169** was immediately subjected to reduction using ten molar equivalents of $TiCl_3 \cdot 3THF$ in the presence of ammonium acetate which afforded indole **170**. Compound **170** was transformed to the target molecule (±)-apsidospermidine **171** in a further three steps.[46-47]

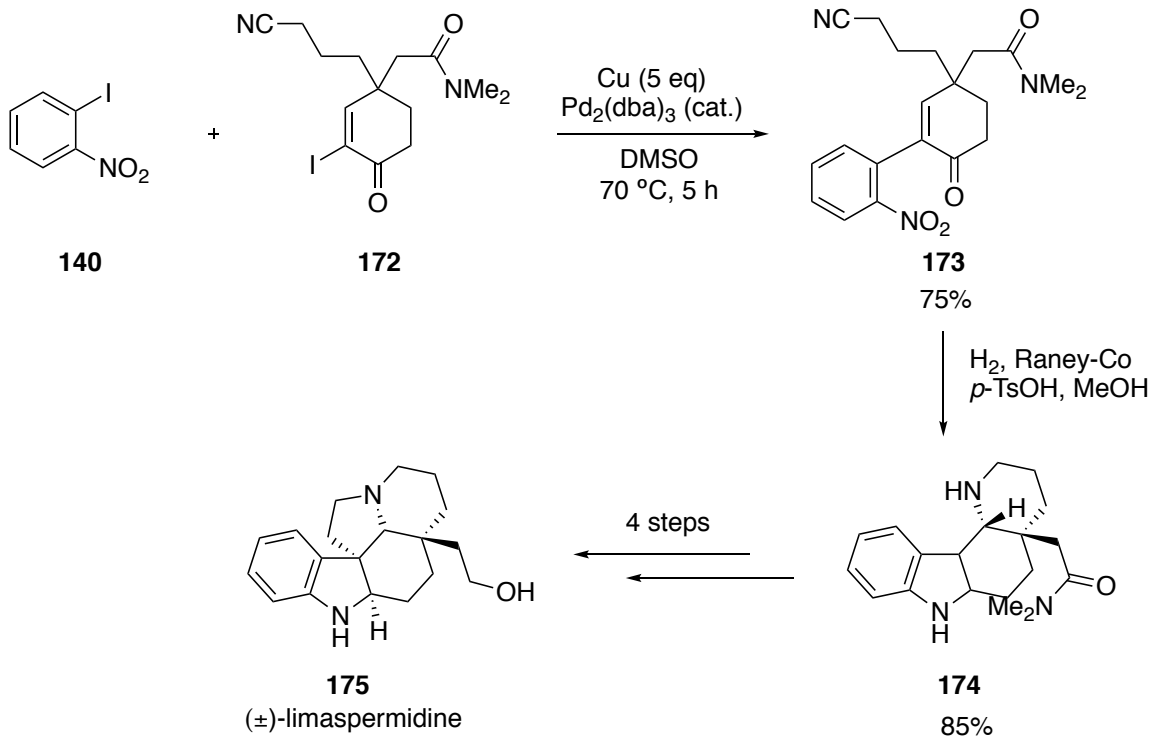


Scheme 35 Banwell and Lupton's synthesis of (±)-apsidospermidine

1.6.2 Synthesis of (±)-limaspermidine

The Pd[0]-catalysed Ullmann cross-coupling reaction was also a crucial step in the synthesis of the *apsidosperma* alkaloid (±)-limaspermidine (Scheme 29, **175**).[48] In four steps, the relevant α-iodocyclohexenone **171** was prepared and coupled with commercially available *o*-iodonitrobenzene (**140**) using five equivalents of copper powder, catalytic $Pd_2(dba)_3$ and DMSO as the solvent at 70 °C for 0.5 h. The resulting

compound **173** was subjected to a pivotal reductive cyclisation using a large excess of Raney-cobalt in methanol and five molar equivalents of *p*-TsOH, which resulted in the exclusive formation of the *cis*-ring fused product **174**. A further four steps afforded the natural product (±)-limaspermidine (**175**).

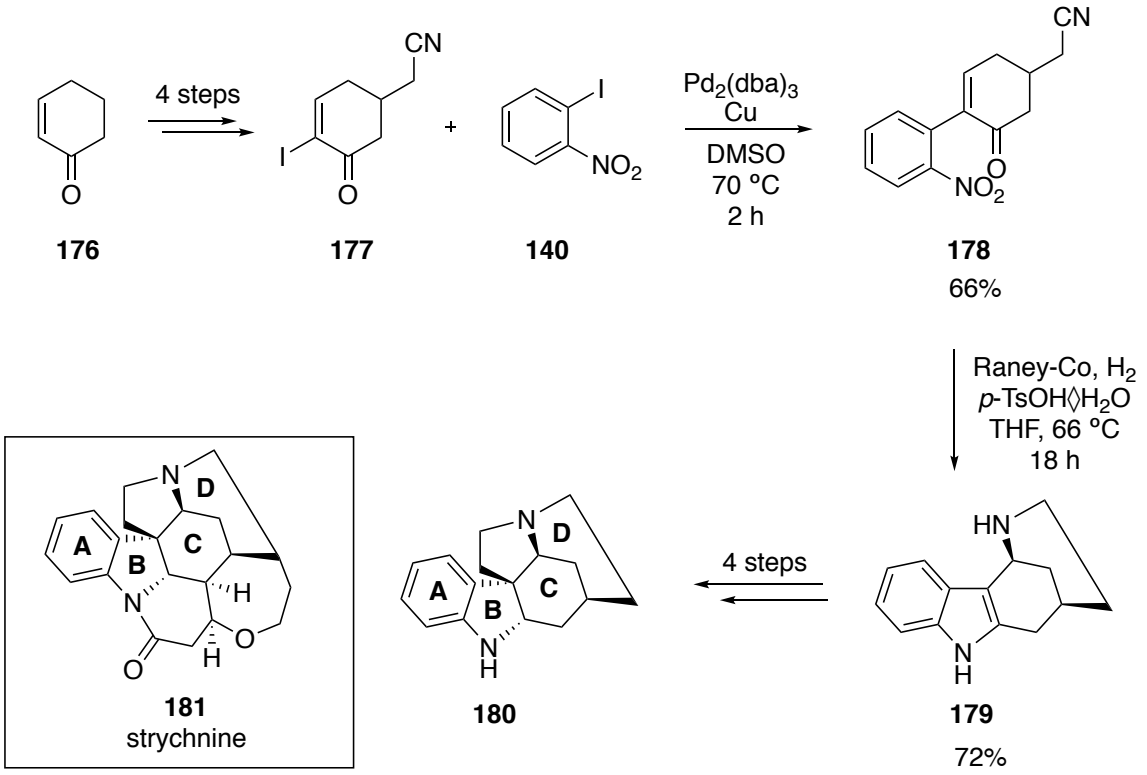


Scheme 36 Banwell and Tan's synthesis of (±)-limaspermidine

1.6.3 Synthesis of the ABCD-ring substructure of strychnine

Work by Reekie and Banwell towards the synthesis of strychnine used the key Pd[0]-catalysed Ullmann cross-coupling and a Raney cobalt-mediated tandem reductive cyclisation to construct the ABCD-ring substructure of strychnine (**Scheme 30**, **181**).[49] The commercially available cyclohexenone **186** was converted in four steps to the desired cyclic enone **177** and subsequently subjected to Pd[0]-catalysed Ullmann cross-coupling conditions with *o*-iodoonitrobenzene (**140**) to afford the α-arylcyclohexenone **178**. Refluxing a solution of compound **178**, Raney-cobalt and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) under an atmosphere of hydrogen gave the desired tetracyclic ABCD-ring system of the *Strychnos* alkaloid family, compound **179**. The E

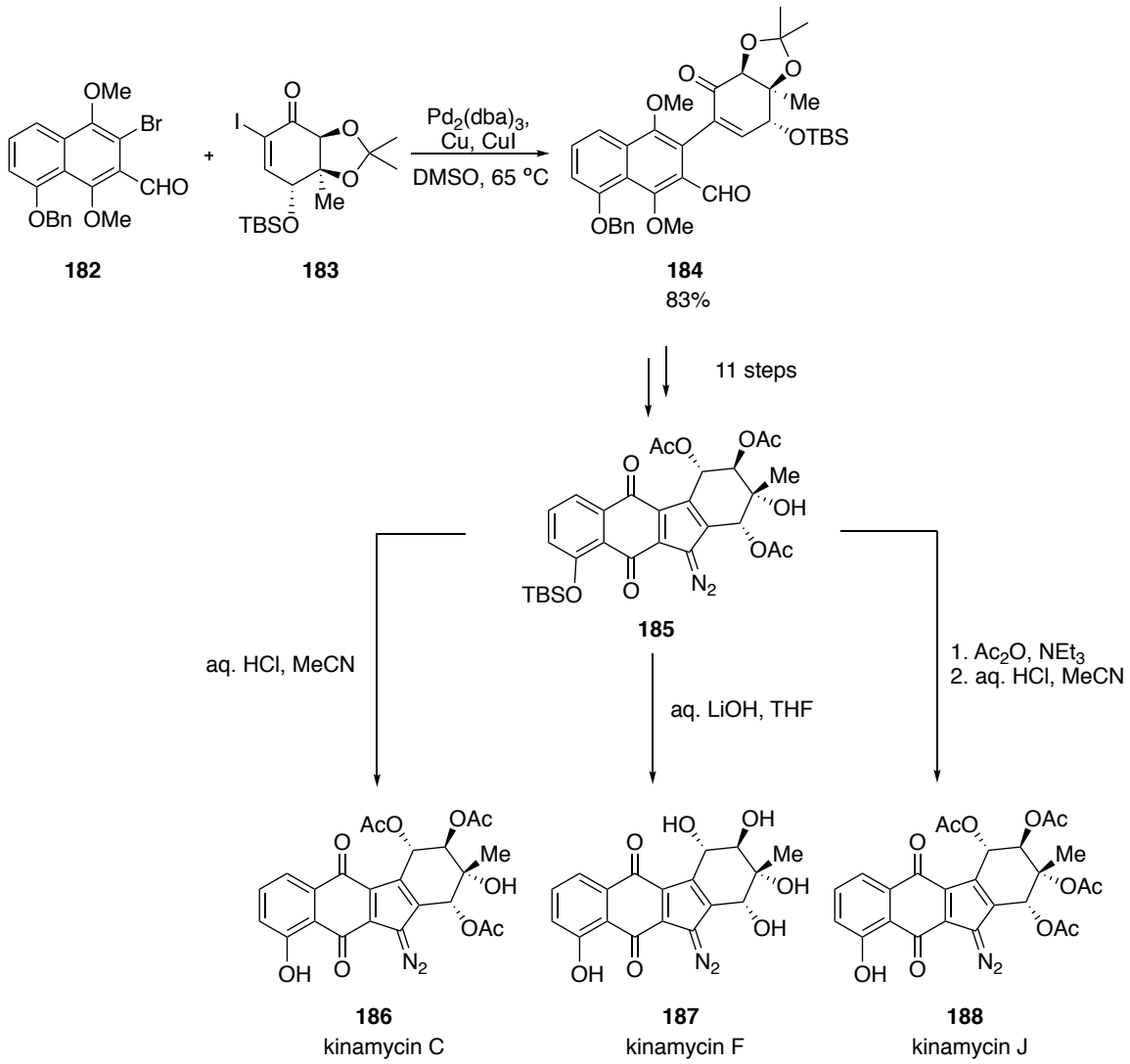
ring can be constructed in an additional 4 steps to give the western hemisphere of strychnine, compound **180**.



Scheme 37 Reekie and Banwell's synthesis of the ABCD-ring substructure of strychnine

1.7 Recent literature on Pd[0]-catalysed Ullmann Cross-coupling Reactions

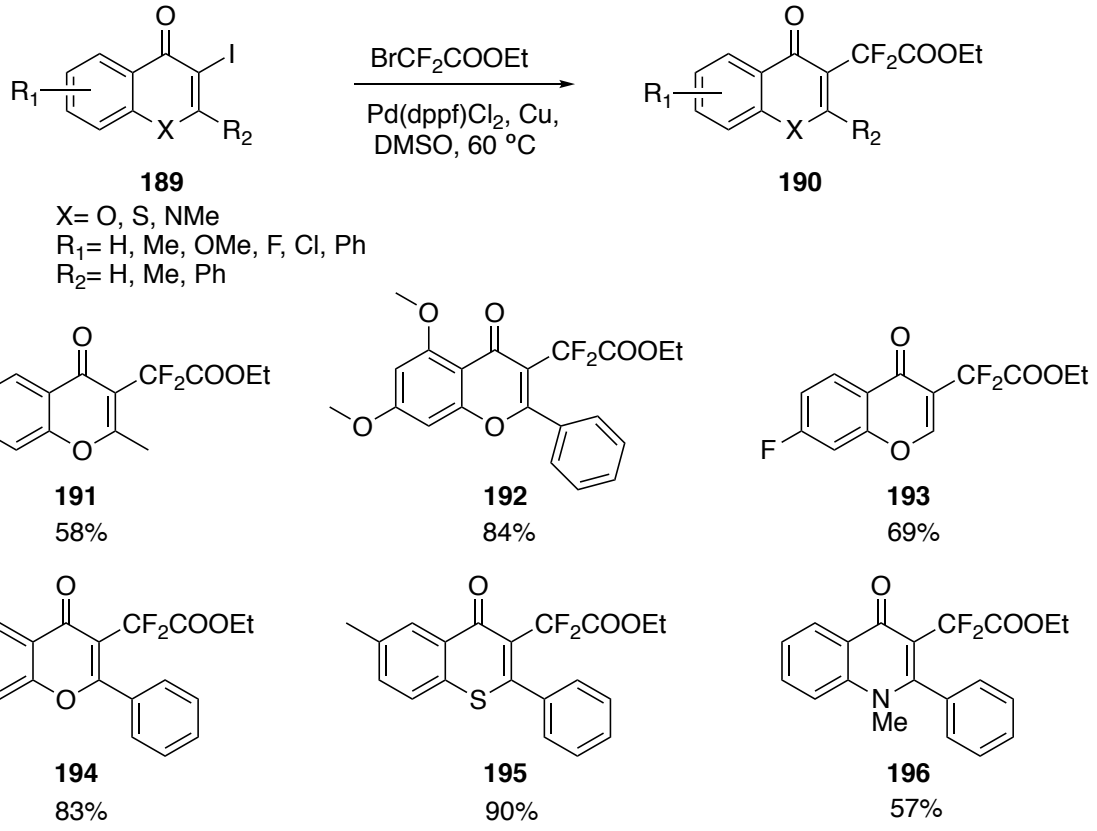
In 2007, Nicolaou and co-workers synthesised kinamycins C (**186**), F (**187**) and J (**188**) using the Pd[0]-catalysed Ullmann cross-coupling protocol developed by the Banwell group as a key step (**Scheme 31**).[50] The required bromo-aldehyde B **182** was prepared in five steps and the enantiomerically pure iodoenone coupling partner **183** was prepared in six steps. Both starting materials were prepared on a multigram scale and subjected to Ullmann conditions to give the cross-coupled product **184** in 83% yield. A further 11 steps gave the key intermediate **185**, which after exposure to aq. HCl in acetonitrile provided kinamycin C (**186**). LiOH-mediated removal of all protecting groups of the intermed



Scheme 38 Kinamycin synthesis via Pd[0]-catalysed Ullmann cross-coupling reaction

iate **185** gave kinamycin F **187**. Acetylation of compound **185**, followed by TBS-ether cleavage (aq. HCl, acetonitrile) furnished kinamycin J (**188**).

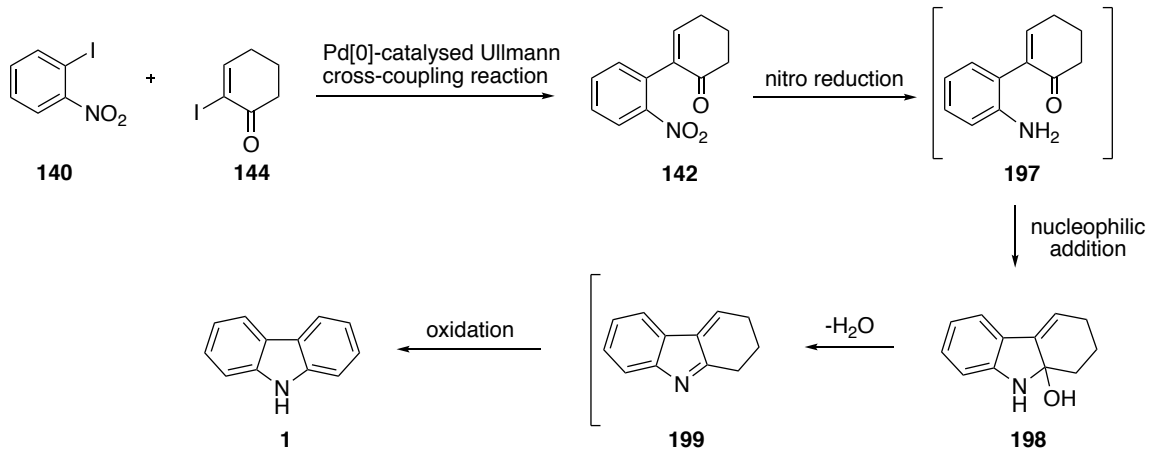
Han and co-workers[51] applied this strategy to the cross-coupling of 3-iodochromones, thiochromones and quinolones with ethyl bromodifluoroacetate (**Scheme 32**) to provide a succinct method for the construction of 3-ethoxycarbonyldifluoromethyl chromones, thiochromones, and quinonolones. Optimum conditions were developed using 5% $Pd(dppf)Cl_2$, two equivalents of $BrCF_2COOEt$, four equivalents of copper powder and DMSO at 60 °C. This reaction is compatible with a variety of functional groups including electron-donating methyl, methoxy, and aryl groups as well as electron-withdrawing fluorinated and chlorinated substituents.



Scheme 39 Aryl difluoroacetates prepared via the Pd[0]-catalysed Ullmann cross-coupling of 189 and $BrCF_2COOEt$

1.8 Our Proposed Approach to Carbazoles

Given the robust nature of the Pd[0]-Ullmann cross-coupling protocol, we proposed that it could be used as a key step for in the synthesis of carbazoles, We proposed first involve the Pd[0]-catalysed Ullmann cross-coupling reaction between an α-halogentated, α,β-unsaturated cyclic enone **140** and an *o*-haloarene **144** to afford compound **142**. Through careful choice of reduction conditions, based on research conducted through the group as outlined in prior chapters, the nitro moiety could be reduced while preserving the double bond from the cyclic enone, thus providing amine **197**. After intramolecular Schiff base formation, it was envisaged that a spontaneous oxidation could occur to give the desired carbazole (**1**), (**Scheme 33**).



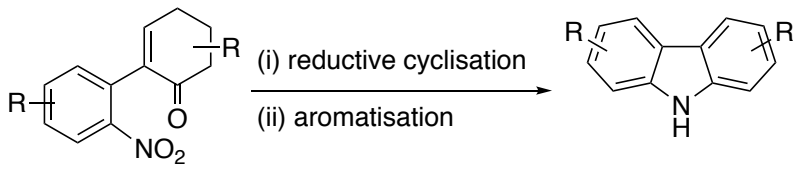
Scheme 40 Our proposed carbazole synthesis via a Pd[0]-catalysed Ullmann cross-coupling reaction.

1.9 Thesis Overview

This thesis details two publications that examines the proposed approach to carbazole synthesis. Publication 1 examines the Ullmann cross coupling for the synthesis of carbazole derivatives. Publication 2 builds upon this work to generate a range of carbolines.

Publication 1: A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A.

The first publication arising from this thesis explores the synthesis of compounds of type **200** with various R substitutions utilising the Pd-catalysed Ullmann cross-coupling. Subjecting these compounds to a reductive cyclisation followed by aromatisation generates carbazoles **201** with various substitution patterns (**Scheme 34**). This methodology was also used to generate natural products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A.

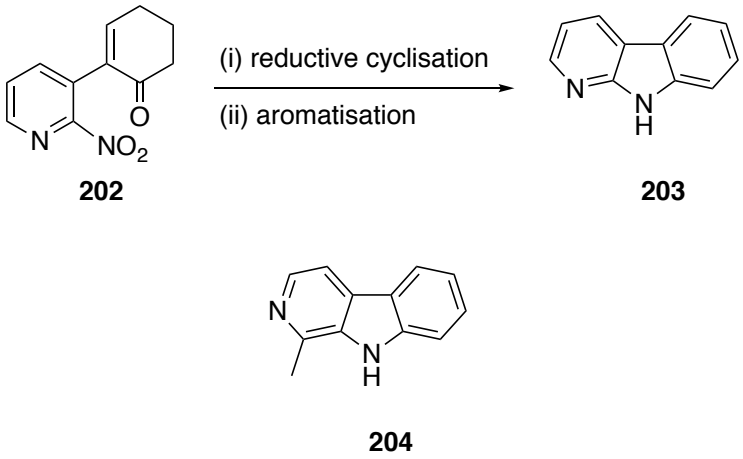


200 **201**

Scheme 34 Summary of Publication 1, a new synthetic approach to carbazoles.

Publication 2: A Unified Approach to the Isomeric *α*-, *β*-, *γ*-, and *δ*-Carbolines via their 6,7,8,9-Tetrahydro Counterparts

In the second publication arising from this thesis, building upon the above mentioned publication, we were able to generate compound **202**. Subjecting thise compounds to a reductive cyclisation followed by aromatisation generates α-carboline **203** (**Scheme 35**). Compound **202** as its various *N*-regioisomers were also synthesised allowing access to β-, γ-, and δ-carbolines. This methodology was also used to generate natural product, β-carboline containing harman (**204**).



202 **203** **204**

Scheme 35 Summary of Publication 2, a new synthetic approach to carbolines.

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Publication 1.

A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A.

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A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9*H*-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine A

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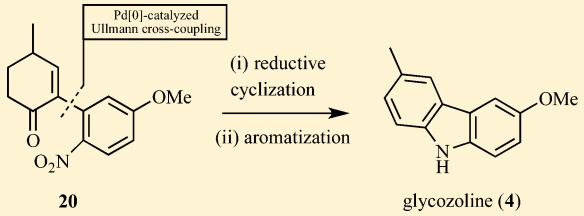
Supporting Information

ABSTRACT: The title natural products **2**–**7** have been prepared by reductive cyclization of the relevant 2-arylcyclohex-2-en-1-one (e.g. **20**) to the corresponding tetrahydrocarbazole and dehydrogenation (aromatization) of this to give the target carbazole (e.g. **4**). Compounds such as **20** were prepared using a palladium-catalyzed Ullmann cross-coupling reaction between the appropriate 2-iodocyclohex-2-en-1-one and *o*-halonitrobenzene.



INTRODUCTION

9*H*-Carbazole (**1**) (Figure 1) was first isolated from coal tar more than 100 years ago,[1] and since that time this aromatic

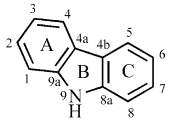


Figure 1. Structure of parent 9*H*-carbazole (**1**) and the associated ring labeling and atom numbering.

heterocycle and its various derivatives have fascinated organic chemists because of their value in both medicine and materials science.[2] Many biologically active natural products embodying this framework have also been isolated, particularly from higher plants.[2d,e,3] As such, the development of methods for the synthesis of the carbazoles has been an ongoing field of research. A suite of approaches to these compounds has been reported, ranging from the classical Fischer–Borsche[4] and Graebe–Ullmann[5] routes to more contemporary ones such as the cyclization of biarylnitrenes (Cadogan synthesis)[6] or variants thereof and the annulation of indoles,[7] including through electrocyclization processes. Despite the demonstrated utility of these and other approaches,[8] perhaps the most effective route to carbazoles involves the cyclization of diarylamines, especially under oxidative conditions.[9] Variations on this last approach have been used to great effect in developing total syntheses of a plethora of carbazole-containing natural products, with particularly notable contributions having being made, especially in recent times, by the Knölker group.[2,9e–i,k,m]

Sometime ago we reported[10] that 1,2,3,4-tetrahydro-9*H*-carbazoles (formally 2,3,4,9-tetrahydro-1*H*-carbazoles) can be formed by a two-step process involving an initial the palladium-catalyzed Ullmann cross-coupling of 2-halocyclohex-2-en-1-ones with *o*-halonitrobenzenes and then subjecting the resulting 2-arylcyclohex-2-en-1-ones to a reductive cyclization reaction.[11] Since various methods are available for or could be applied to the oxidation of tetrahydrocarbazoles to carbazoles,[12] we sought to establish if the reaction sequence just mentioned could provide a useful means for obtaining natural products embodying the latter ring system. Herein we report the outcomes of such studies and by which means we have been able to realize syntheses of the parent carbazole (**1**) as well as the natural products 3-methyl-9*H*-carbazole (**2**),[13] glycoborine (**3**, aka glycrophylamine),[3a,14] glycozoline (**4**),[3a,15] clauszoline K (**5**),[16] mukonine (**6**),[17] and karapinchamine A (**7**)[18] together with their monomethoxylated congener **8** (Figure 2).

RESULTS AND DISCUSSION

Our initial studies focused on acquiring targets **1** and **2**, and this involved (Scheme 1) the initial palladium-catalyzed Ullmann cross-coupling of 2-iodocyclohex-2-en-1-one (**9**)[19] or its C4-methylated counterpart **10**[11] with commercially available *o*-bromonitrobenzene (**11**) under conditions defined earlier,[10] and thereby affording the anticipated and previously reported 2-arylcyclohex-2-en-1-ones **12**[10,11] (85%) and **13**[11] (86%), respectively. A methanolic solution of each of compounds **12** and **13** was then subjected to reaction with hydrogen in the presence of commercially available W-2 Raney nickel at room temperature, and so affording the tetrahydrocarbazoles **14**[10,11,12b] (64%) and **15**[11,12b] (58%), respectively. Various

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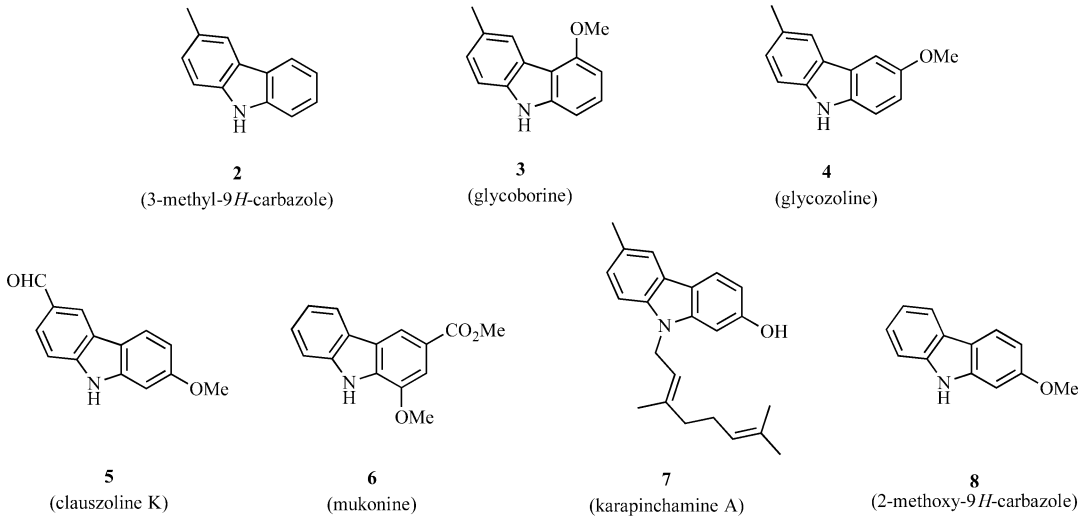
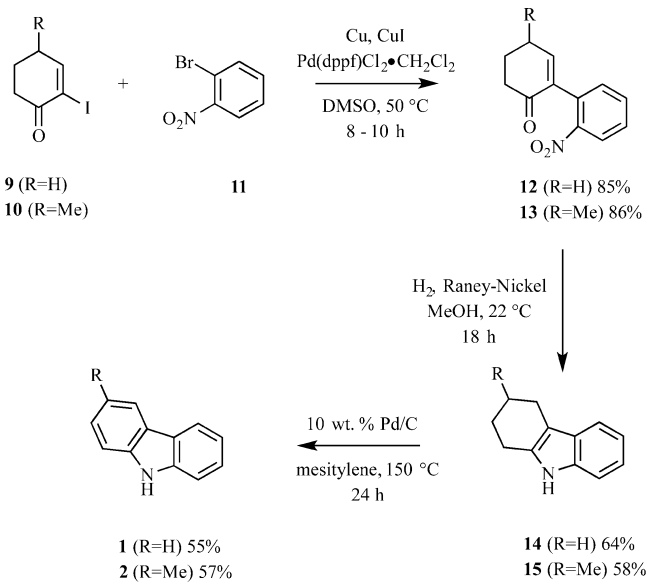
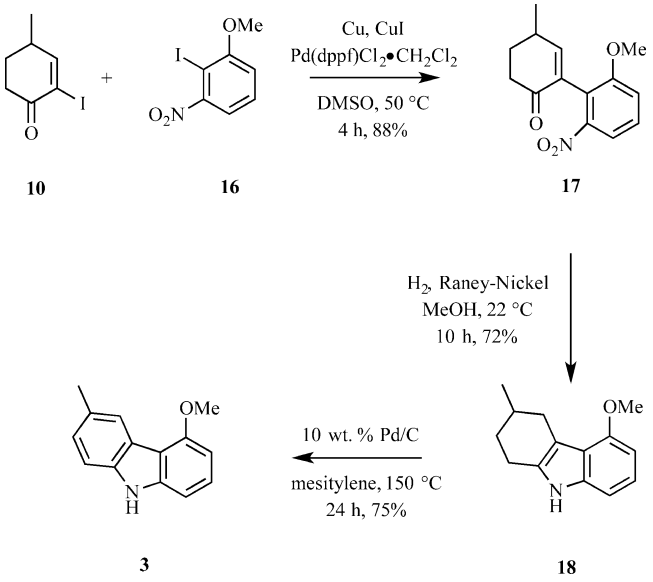


Figure 2. Structures of natural products **2**-**7** and the monosubstituted congener **8**.

Scheme 1. Reaction Sequences Leading to Carbazoles 1 and 2



Scheme 2. Synthesis of Glycoborine (3)



attempts to modify these reductive cyclization conditions in an effort to obtain dihydrocarbazoles (or perhaps even the carbazoles themselves as a result of conducting the workup under aerobic conditions) were unsuccessful. In the final step of the reaction sequence, then, mesitylene solutions of compounds **14** and **15** were each heated to 150 °C with an equal weight of 10% palladium on carbon, and thus affording carbazoles **1** (55%) and **2**[12b] (57%), respectively. All of the spectroscopic and physical data acquired on these reaction products were in complete accord with the assigned structures and matched those derived from a commercially available sample (in the former case) or reported[6h,12b] in the literature (in the latter case). Furthermore, each was subjected to single-crystal X-ray analysis.[20]

The preparation of glycoborine (**3**), a synthetic target pursued by others,[6e,g,k,9h,k,14] was readily accomplished as shown in Scheme 2 by coupling 2-iodo-4-methylcyclohex-2-en-1-one (**10**)[11] with nitroarene **16**[21] and thereby producing the arylated cyclohexenone **17** (88%), the structure of which was secured by a single-crystal X-ray analysis.[20] The appearance of 28 signals in the ^{13}C NMR spectrum of this C_{14} compound suggested that it existed as diastereoisomeric atropisomers under ambient conditions. Reductive cyclization of compound **17** using hydrogen in the presence of W-2 Raney nickel gave the tetrahydrocarbazole **18**[11a] (72%), and dehydrogenation of this compound under the same conditions as employed before then afforded the target natural product **3**, that was obtained in 75% yield. Once again, all of the appropriate spectral comparisons left no doubt that the glycoborine had been obtained but final confirmation of this followed from a single-crystal X-ray analysis.[20]

A reaction sequence essentially analogous to that described above was used to synthesize glycozoline (**4**), a compound that has also been the target of previous studies.[3c,4c,6i,12b,22] Thus, as shown in Scheme 3, reaction of 2-iodo-4-methylcyclohex-2-en-1-one (**10**) with commercially available nitroarene **19** under the by now standard palladium-catalyzed Ullmann cross-coupling conditions gave the anticipated product **20** (87%), which was reductively cyclized with hydrogen in the presence of W-2

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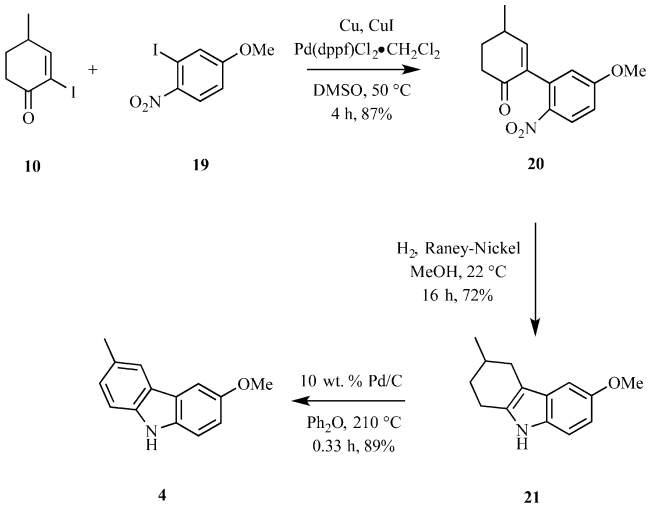
Scheme 3. Synthesis of Glycozoline (4)

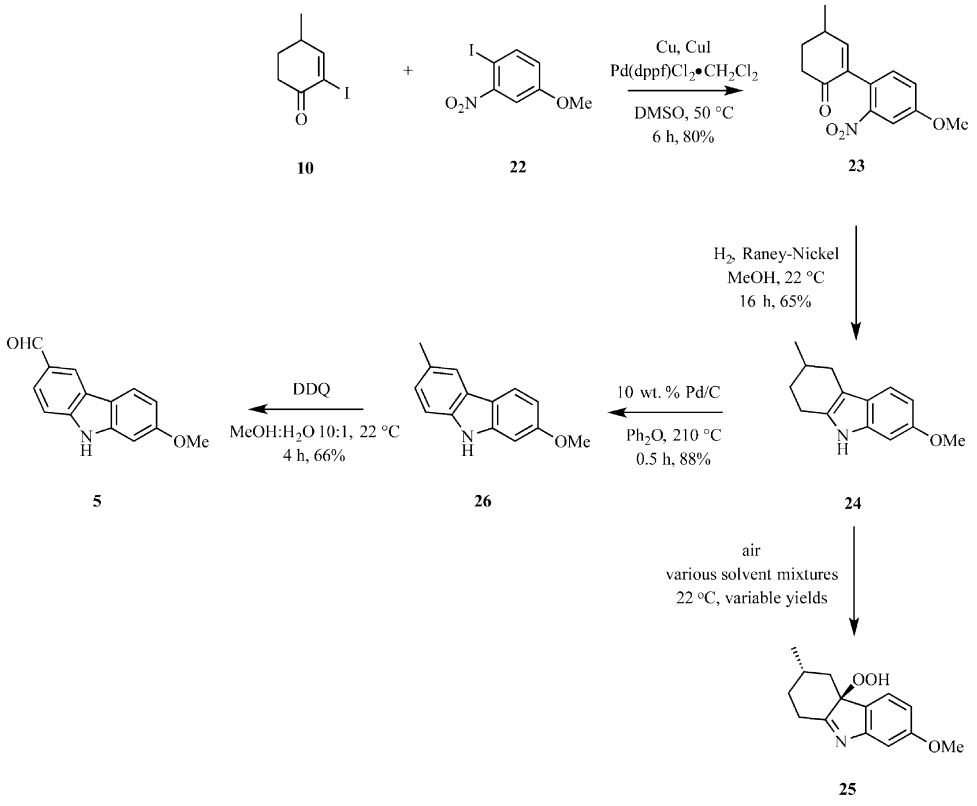


Raney nickel and so providing the tetrahydrocarbazole **21**[12b,d,22b] in 72% yield. Dehydrogenation of compound **21** through brief treatment with 10% Pd on C in diphenyl ether at 210 °C then gave glycozoline (**4**) in 89% yield, the structure of which was confirmed by single-crystal X-ray analysis.[20]

The reaction sequence leading to clauszoline K (**5**) (Scheme 4), another popular target,[22d,23] provided some insights into the propensity of 2,3,4,9-tetrahydro-1*H*-carbazoles to engage in alternate oxidation reactions.[12a] Thus, the palladium-catalyzed Ullmann cross-coupling of the iodinated cyclohexenone **10** with the commercially available 2-iodonitroarene **22** proceeded as anticipated to give the required arylated cyclohexenone **23** (80%), and this in turn engaged in the same type of reductive cyclization reaction as seen before to give tetrahydrocarbazole **24**[11a,14] (65%). However, compound **24** proved rather prone to oxidation, with the hydroperoxide **25** being formed in increasing quantities when its precursor was allow to stand at 22 °C as a solution (in various solvents) left open to the atmosphere. Compound **25**, the structure of which was established by single-crystal X-ray analysis,[20] may arise through a facially selective ene reaction between indole **24** and singlet oxygen, the latter reactant (most likely) being produced through the other (**24**) serving as a sensitizer. Despite the ease of the conversion **24** → **25**, the tetrahydrocarbazole was readily dehydrogenated in the same manner as described in the other instances reported herein, producing carbazole **26**[9c,h,22d,23a,b] in 88% yield. Unlike isomer **4**, compound **26** is not a naturally occurring material but is readily converted into one, namely aldehyde **5** (clauszoline K) (66%), on treatment with DDQ in aqueous methanol[9h,23a,b] at ambient temperature for 4 h. The structure of compound **5** was confirmed by single-crystal X-ray analysis.[20]

The carbazole natural product mukonine (**6**), another popular target compound,[9a,12d,17a,24] carries both the methoxy and carbomethoxy substituents in the same ring and so requiring, as the first step in the present synthesis, the palladium-catalyzed Ullmann cross-coupling of the "parent" 2-iodocyclohexeneone **9** with the readily obtained (see below) tetrasubstituted arene **27** (Scheme 5), affording the required 2-arylated cyclohexenone **28**, albeit in just 39% yield. Reductive cyclization of compound **28** under standard conditions gave tetrahydrocarbazole **29** (79%), which upon dehydrogenation under the usual conditions afforded mukonine (**6**) (66%) as a white, crystalline solid. Once again, all of the derived spectral

Scheme 4. Synthesis of Clauszoline K (5)



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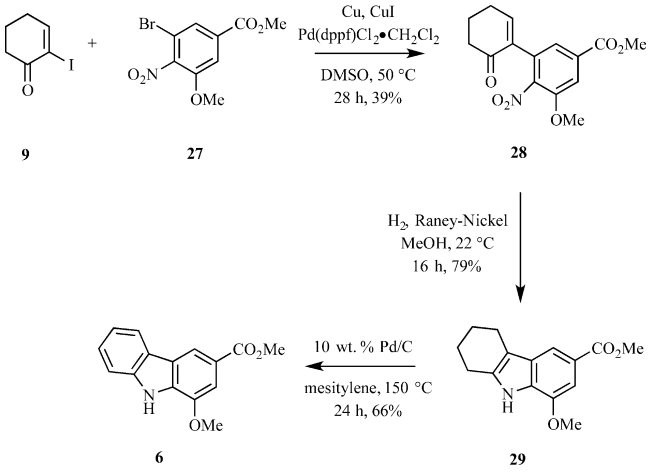
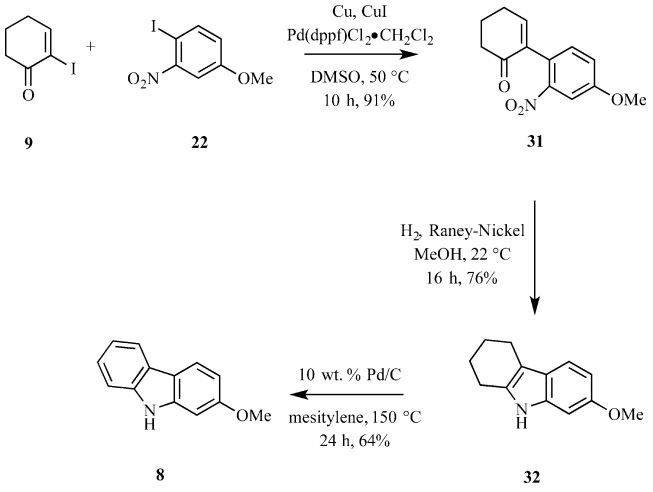
Scheme 5. Synthesis of Mukonine (6)



Scheme 7. Synthesis of 2-Methoxy-9*H*-carbazole (8)



data were fully consistent with the assigned structure as well as those reported for the natural product, but final confirmation of this followed from a single-crystal X-ray analysis.[20] The arene **27** used in this sequence was prepared by first brominating commercially available methyl 4-amino-3-methoxybenzoate with *N*-bromosuccinimide (NBS) and then oxidizing the previously reported[25] bromide to the corresponding nitro compound (viz. **27**) using *m*-chloroperbenzoic acid (*m*CPBA) (see the Experimental Section for details).

The trisubstituted carbazole natural product karapinchamine A (**7**), the subject of just one previous synthetic study,[7e] was readily obtained (Scheme 6) by treating compound **26** with boron tribromide so as to effect cleavage of the methyl ether moiety and then treating the product hydroxycarbazole **30**[9h] (84%), as a solution in THF, with an excess of *n*-butyllithium and then ca. 1.5 equiv of geranyl bromide. By such means karapinchamine A (**7**) was obtained in 50% yield after column chromatography. Interestingly, there was no evidence for the formation of the isomeric *O*-geranylated product during the course of this reaction. All of the spectral data acquired on product **7** matched those recorded for the natural product (see the Supporting Information for relevant spectral comparisons).

Monosubstituted carbazoles wherein the single substituent derives from the arene coupling partner are also readily available by the procedures reported here. Thus, as shown in Scheme 7, cross-coupling of compounds **9** and **22** under the usual conditions afforded enone **31**[10,11b] (91%), which on subjection to reductive cyclization using hydrogen in the presence of Raney nickel afforded the tetrahydrocarazole **32**[10,11b,26] (76%). Dehydrogenation of compound **32** using 10% Pd on C in hot mesitylene then afforded carbazole **8**[6f,k,l,9j] (64%), the spectral data for which matched those reported previously.

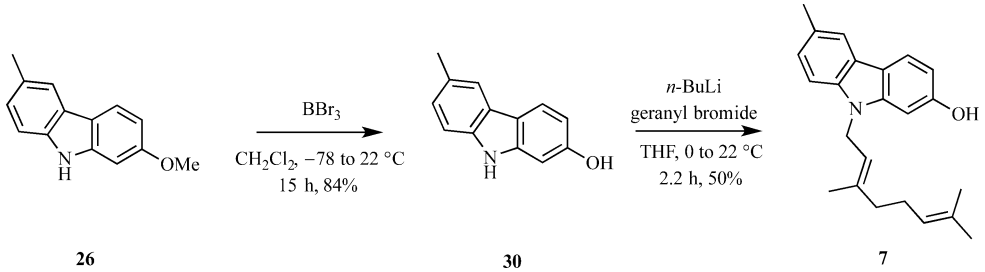
CONCLUSIONS

The procedures detailed here allow for the straightforward preparation, in a fully regiocontrolled manner, of a range of carbazoles carrying various combinations of substituents in both the A and the C rings as well as on the nitrogen of the B ring. Substitution patterns encountered in naturally occurring and biologically active carbazoles appear to be completely accessible using the methods described here. As a further indication of the utility of the title protocol, it is worth noting that carbazole **30** is an established precursor to the pyrano[3,2-*a*]carbazole alkaloids isogirinimbine and mahanimbicine.[9h] In a related vein, clauszoline K (**5**) is an established synthetic precursor to the alkaloids clauszoline M and N (the corresponding methyl ester and acid, respectively).[22d,23a] The present study also serves to highlight the continued utility of the palladium-catalyzed Ullmann cross-coupling reaction,[27] especially when it is used in combination with reductive cyclization protocols.[28]

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral], where multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet, or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet"

Scheme 6. Synthesis of Karapinchamine A (7)



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appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double-focusing, triple-sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in either positive or negative ion mode. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concentrated)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid (concentrated)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[29] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e. after they had crystallized from the concentrated chromatographic fractions). Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. The copper powder used in the palladium-catalyzed Ullmann cross-coupling reactions had a particle size of <75 μm. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[30] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *2-Iodocyclohex-2-en-1-one (**9**).* Following a procedure reported by Johnson et al.,[31] a magnetically stirred solution of cyclohex-2-en-1-one (2.00 g, 20.8 mmol) in chloroform/pyridine (80 mL of a 1/1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 2 h, with a solution of molecular iodine (18.5 g, 72.8 mmol) in chloroform/pyridine (80 mL of a 1/1 v/v mixture). The ensuing mixture was warmed to 22 °C, stirred at this temperature for 16 h then diluted with diethyl ether (200 mL) and washed with water (1 × 100 mL), $Na_2S_2O_3$ (2 × 100 mL of a 20% w/v aqueous solution), HCl (2 × 100 mL of a 1 M aqueous solution), water (2 × 100 mL) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This was subjected to flash column chromatography (silica, 2/5/70 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), 2-iodocyclohex-2-en-1-one **9**[19] (3.85 g, 83%) as a light yellow solid, mp 47−50 °C (lit.[19] mp 47−49 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 4.4 Hz, 1H), 2.67 (m, 2H), 2.44 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 159.6, 104.0, 37.4, 30.1, 23.0; IR ν_{max} 2949, 2939, 1675, 1585, 1421, 1314, 1120, 966, 914, 803, 703 cm^{-1}; MS (EI, 70 eV) m/z 222 ($M^{+\bullet}$, 100%), 194 (75), 67 (40); HRMS $M^{+\bullet}$ calcd for $C_6H_7{}^{127}IO$ 221.9542, found 221.9540.

*2-Iodo-4-methylcyclohex-2-en-1-one (**10**).* A magnetically stirred solution of 4-methylcyclohex-2-en-1-one[32] (2.29 g, 20.8 mmol) in chloroform/pyridine (80 mL of a 1/1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 2 h, with a solution of molecular iodine (18.5 g, 72.8 mmol) in chloroform/pyridine (80 mL of a 1/1 v/v mixture). The ensuing mixture was warmed to 22 °C, stirred at this temperature for 16 h, and then diluted with diethyl ether (200 mL) and washed with water (1 × 100 mL), $Na_2S_2O_3$ (2 × 100 mL of a 20% w/v aqueous solution), HCl (2 × 100 mL of a 1 M aqueous solution), water (2 × 100 mL), and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 1/19 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.5 in 1/5 v/v ethyl acetate/40−60 petroleum ether), compound **10**[11b] (3.98 g, 81%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.6 Hz, 1H), 2.66−2.56 (complex m, 2H), 2.48−2.39 (complex m, 1H), 2.07 (m, 1H), 1.64 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 164.7, 102.9, 35.6, 35.5, 30.6, 19.7; IR ν_{max} 2959, 2930, 2870, 1686, 1585, 1454, 1318, 1109, 790 cm^{-1}; MS (EI, 70 eV) m/z 236 ($M^{+\bullet}$, 100%), 208 (25), 109 (75), 81 (50), 53 (60); HRMS $M^{+\bullet}$ calcd for $C_7H_9{}^{127}IO$ 235.9698, found 235.9691.

*2′-Nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**12**).* A magnetically stirred mixture of *o*-bromonitrobenzene (**11**) (941 mg, 4.7 mmol), 2-iodocyclohex-2-en-1-one (**9**) (470 mg, 2.1 mmol), copper powder (673 mg, 10.6 g atom), CuI (605 mg, 3.2 mmol), and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (87 mg, 0.1 mmol) in deoxygenated DMSO (21 mL) maintained under nitrogen was heated to 50 °C for 10 h. The reaction mixture was then cooled to room temperature, quenched with water (1 × 20 mL), diluted with ethyl acetate (1 × 40 mL), and filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 50 mL), and the filtrate was washed with water (2 × 100 mL) and then brine (2 × 100 mL). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil, and subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in 1/1 v/v ethyl acetate/40−60 petroleum ether), compound **12**[10,11] (390 mg, 85%) as a light yellow crystal, mp 96−99 °C (lit.[10] mp 92−95 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 1H), 7.58 (m, 1H), 7.46 (m, 1H), 7.25 (m, 1H), 7.00 (t, J = 4.2 Hz, 1H), 2.56 (m, 4H), 2.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 148.7, 146.8, 139.4, 133.4, 132.2, 131.8, 128.8, 124.2, 38.4, 26.4, 22.7; IR ν_{max} 2949, 2868, 1679, 1523, 1353, 1158, 859, 788, 751, 709 cm^{-1}; MS (ESI, +ve) m/z 240 [$(M + Na)^+$, 100%], 218 [$(M + H)^+$, 10]; HRMS $(M + H)^+$ calcd for $C_{12}H_{12}NO_3$ 218.0817, found 218.0825.

*5-Methyl-2′-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**13**).* A magnetically stirred mixture of *o*-bromonitrobenzene (**11**) (960 mg, 4.75 mmol), 2-iodo-4-methylcyclohex-2-en-1-one (**10**) (510 mg, 2.16 mmol), copper powder (687 mg, 10.80 g atom), CuI (617 mg, 3.24 mmol), and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (88 mg, 0.11 mmol) in deoxygenated DMSO (22 mL) was heated to 50 °C under a nitrogen atmosphere for 8 h. The reaction mixture was then cooled to room temperature, quenched with water (20 mL), diluted with ethyl acetate (40 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 50 mL), and the organic phase associated with the filtrate was then washed with water (2 × 100 mL) and brine (2 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.5 in 1/1 v/v ethyl acetate/40−60 petroleum ether), compound **13**[11] (430 mg, 86%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 1H), 7.58 (m, 1H), 7.45 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 2.79 (broad s, 1H), 2.65−2.47 (complex m, 2H), 2.20 (m, 1H), 1.86−1.76 (complex m, 1H), 1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 152.3, 148.7, 138.4, 133.4, 132.1, 131.8, 128.9, 124.3, 37.2, 31.8, 30.7, 20.4; IR ν_{max} 2960, 2872, 1681, 1525, 1354, 1159, 788, 750 cm^{-1}; MS (ESI, +ve) m/z 254 [$(M + Na)^+$, 100%], 232 [$(M + H)^+$, 10]; HRMS $(M + Na)^+$ calcd for $C_{13}H_{13}NNaO_3$ 254.0793, found 254.0799.

*2,3,4,9-Tetrahydro-1H-carbazole (**14**).* A magnetically stirred mixture of compound **12** (100 mg, 0.46 mmol) and commercially available W-2 Raney nickel (200 mg, washed twice with absolute ethanol) in methanol (23 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 18 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 30 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 1/5 v/v ethyl

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acetate/40−60 petroleum ether), compound **14**[10,11,12b] (50 mg, 64%) as a white solid, mp 104−106 °C (lit.[12b] mp 104−106 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.70 (broad s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.02−6.92 (complex m, 2H), 2.73 (t, J = 5.9 Hz, 2H), 2.68−2.65 (complex m, 2H), 1.92−1.81 (complex m, 4H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 137.1, 135.1, 128.8, 121.1, 119.1, 118.0, 111.3, 109.7, 24.2, 24.0, 23.8, 21.7; IR ν_{max} 3396, 2926, 2849, 1467, 1450, 1439, 1325, 1304, 1233, 736, 635 cm^{-1}; MS (ESI, +ve) m/z 226 [(M + MeOH + Na)$^+$, 100%], 188 (56), 172 [(M + H)$^+$, 70]; HRMS (M + H)$^+$ calcd for $C_{12}H_{14}N$ 172.1126, found 172.1121.

*3-Methyl-2,3,4,9-tetrahydro-1H-carbazole (**15**).* A magnetically stirred mixture of compound **13** (320 mg, 1.38 mmol) and commercially available W-2 Raney nickel (640 mg, washed twice with absolute ethanol) in methanol (69 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 18 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 30 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1/5 v/v ethyl acetate/40−60 petroleum ether), compound **15**[11,12b] (148 mg, 58%) as a white solid, mp 98−100 °C (lit.[12b] mp 98−100 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.70 (broad s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.02−6.92 (complex m, 2H), 2.83−2.75 (complex m, 3H), 2.24 (m, 1H), 1.98−1.86 (complex m, 2H), 1.53 (m, 1H), 1.13 (d, J = 6.6 Hz, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 137.4, 134.9, 128.7, 121.1, 119.1, 118.0, 111.3, 109.7, 32.3, 30.6, 30.2, 23.4, 22.1; IR ν_{max} 3405, 2949, 2923, 1620, 1467, 1326, 1232, 1009, 740 cm^{-1}; MS (ESI, +ve) m/z 240 [(M + MeOH + Na)$^+$, 100%], 202 (45), 186 [(M + H)$^+$, 30]; HRMS (M + H)$^+$ calcd for $C_{13}H_{16}N$ 186.1283, found 186.1286.

*9H-Carbazole (**1**).* A magnetically stirred mixture of compound **14** (46 mg, 0.27 mmol) and 10 wt % Pd/C (46 mg) in mesitylene (5 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The filtrate was concentrated under reduced pressure, and the ensuing mixture of product **1** and mesitylene was then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.6 in 1/5 v/v ethyl acetate/40−60 petroleum ether) then gave compound **1** (25 mg, 55%) as a white, crystalline solid, mp 237−238 °C (lit.[33] mp 245 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 10.32 (broad s, 1H), 8.11 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.39 (m, 2H), 7.18 (m, 2H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 141.0, 126.4, 124.0, 120.9, 119.6, 111.7; IR ν_{max} 3416, 3049, 1597, 1449, 1233, 928, 745, 722 cm^{-1}; MS (ESI, − ve) m/z 166 [(M − H)$^-$, 100%]; HRMS (M − H)$^-$ calcd for $C_{12}H_8N$ 166.0657, found 166.0656.

*3-Methyl-9H-carbazole (**2**).* A magnetically stirred mixture of compound **15** (145 mg, 0.78 mmol) and 10 wt % Pd/C (145 mg) in mesitylene (15 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The filtrate was concentrated under reduced pressure, and the ensuing mixture of product **2** and mesitylene was then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1/3 v/v ethyl acetate/40−60 petroleum ether), compound **2**[12b] (80 mg, 57%) as a white solid, mp 200−202 °C (lit.[12b] mp 205−210 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 10.17 (broad s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.90 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.37−7.33 (complex m, 1H), 7.22 (dd, J = 8.2 and 1.2 Hz, 1H), 7.15 (m, 1H), 2.48 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 141.3, 139.2, 128.6, 127.7, 126.2, 124.2, 123.8, 120.8, 120.7, 119.4, 111.6, 111.4, 21.5; IR ν_{max} 3403, 3050, 2914, 2853, 1605, 1459, 1333, 1238, 805, 746, 726 cm^{-1}; MS (ESI, −ve) m/z 180 [(M − H)$^-$, 100%]; HRMS (M − H)$^-$ calcd for $C_{13}H_{10}N$ 180.0813, found 180.0804.

*2′-Methoxy-5-methyl-6′-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**17**).* A magnetically stirred mixture of 2-iodo-1-methoxy-3-nitrobenzene (**16**)[21] (341 mg, 1.22 mmol), 2-iodo-4-methylcyclohex-2-en-1-one (**10**) (519 mg, 2.20 mmol), copper powder (311 mg, 4.89 g atom), CuI (349 mg, 1.83 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (100 mg, 0.12 mmol) in deoxygenated DMSO (24 mL) was heated to 50 °C under a nitrogen atmosphere for 4 h. The reaction mixture was then cooled to room temperature, quenched with water (10 mL), diluted with ethyl acetate (20 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 25 mL) and the organic phase associated with the filtrate then washed with water (2 × 50 mL) and brine (2 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 2/5/40 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.3 in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), compound **17** (281 mg, 88%) as a light yellow solid, mp 94−96 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.40−7.10 (complex m, 2H), 6.63 (m, 1H), 3.78 (m, 3H), 2.76−2.48 (complex m, 3H), 2.24−2.14 (complex m, 1H), 1.90−1.76 (complex m, 1H), 1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 196.7, 158.1, 158.0, 153.7, 153.5, 150.3, 150.0, 133.0, 132.6, 129.1, 129.2, 121.5, 121.4, 116.1, 116.0, 115.6, 115.4, 56.7, 56.6, 37.3, 37.1, 32.0, 31.6, 30.9, 30.5, 20.4, 20.1; IR ν_{max} 2959, 1674, 1524, 1461, 1351, 1263, 1052, 794, 736 cm^{-1}; MS (ESI, +ve) m/z 284 [(M + Na)$^+$, 100%], 262 [(M + H)$^+$, 15]; HRMS (M + Na)$^+$ calcd for $C_{14}H_{15}NNaO_4$ 284.0899, found 284.0896.

*5-Methoxy-3-methyl-2,3,4,9-tetrahydro-1H-carbazole (**18**).* A magnetically stirred mixture of compound **17** (211 mg, 0.81 mmol) and commercially available W-2 Raney nickel (422 mg, washed twice with absolute ethanol) in methanol (40 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 10 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 15 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/3/30 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.5 in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether), compound **18**[11a] (125 mg, 72%) as a white solid, mp 126−128 °C: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.63 (broad s, 1H), 6.91−6.85 (complex m, 2H), 6.41 (dd, J = 6.5 and 1.9 Hz, 1H), 3.84 (s, 3H), 3.11 (dd, J = 16.0 and 4.7 Hz, 1H), 2.72 (m, 2H), 2.41 (m, 1H), 1.92−1.79 (complex m, 2H), 1.48 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 155.1, 138.8, 132.8, 121.8, 118.6, 109.6, 105.1, 99.7, 55.3, 32.7, 32.1, 30.8, 23.4, 22.2; IR ν_{max} 3397, 2948, 2923, 2836, 1565, 1505, 1349, 1253, 1244, 1104, 775, 729 cm^{-1}; MS (ESI, +ve) m/z 232 (100%), 216 [(M + H)$^+$, 90]; HRMS (M + H)$^+$ calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1393.

*Glycoborine (**3**).* A magnetically stirred mixture of compound **18** (50 mg, 0.23 mmol) and 10 wt % Pd/C (50 mg) in mesitylene (5 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated under reduced pressure, and the ensuing mixture of product **3** and mesitylene was then subjected to flash column chromatography (silica, 2/5/62 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4(5) in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), compound **3**[3a] (35 mg, 75%) as a white solid, mp 130−132 °C (lit.[3a] mp 132.0−134.6 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 10.17 (broad s, 1H), 8.07 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.2 and 1.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.68 (d, J =

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8.0 Hz, 1H), 4.06 (s, 3H), 2.48 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 157.1, 142.7, 138.4, 128.5, 127.2, 126.7, 123.6, 123.5, 113.0, 110.8, 104.7, 100.5, 55.6, 21.6; IR ν_{max} 3402, 2917, 2838, 1608, 1585, 1506, 1459, 1347, 1260, 1098, 750, 723 cm^{-1}; MS (ESI, +ve) *m/z* 234 [(M + Na)$^+$, 10%], 212 [(M + H)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1078.

*5′-Methoxy-5-methyl-2′-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**20**).* A magnetically stirred mixture of commercially available 2-iodo-4-methoxynitrobenzene (**19**) (150 mg, 0.54 mmol), 2-iodo-4-methylcyclohex-2-en-1-one (**10**) (229 mg, 0.97 mmol), copper powder (137 mg, 2.15 g atom), CuI (154 mg, 0.81 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (44 mg, 0.05 mmol) in deoxygenated DMSO (12 mL) was heated to 50 °C under a nitrogen atmosphere for 4 h. The reaction mixture was then cooled to room temperature, quenched with water (5 mL), diluted with ethyl acetate (10 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 15 mL), and the separated organic phase associated with the filtrate was then washed with water (2 × 25 mL) and brine (2 × 25 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 1/3/25 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions [R_f = 0.5(5) in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether], compound **20** (125 mg, 87%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.1 Hz, 1H), 6.90 (dd, *J* = 9.1 and 2.6 Hz, 1H), 6.70 (m, 2H), 3.88 (s, 3H), 2.76−2.51 (complex m, 3H), 2.21 (m, 1H), 1.84 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 163.4, 151.2, 141.7, 139.1, 135.2, 127.2, 117.2, 113.2, 56.1, 37.3, 31.8, 30.8, 20.5; IR ν_{max} 2953, 1681, 1578, 1512, 1340, 1298, 1238, 1026, 844 cm^{-1}; MS (ESI, +ve) *m/z* 284 [(M + Na)$^+$, 100%], 262 [(M + H)$^+$, 10]; HRMS (M + Na)$^+$ calcd for $C_{14}H_{15}NNaO_4$ 284.0899, found 284.0890.

*6-Methoxy-3-methyl-2,3,4,9-tetrahydro-1H-carbazole (**21**).* A magnetically stirred mixture of compound **20** (100 mg, 0.38 mmol) and commercially available W-2 Raney nickel (200 mg, washed twice with absolute ethanol) in methanol (19 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 16 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 10 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/3/20 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether), compound **21**[12b,d,22b] (50 mg, 61%) as a white solid, mp 108−109 °C: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.52 (broad s, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.88 (s, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 3.78 (s, 3H), 2.80−2.73 (complex m, 3H), 2.20 (m, 1H), 1.95−1.85 (complex m, 2H), 1.52 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 154.6, 135.7, 132.5, 129.1, 111.8, 110.7, 109.6, 100.6, 55.8, 32.4, 30.6, 30.4, 23.6, 22.1; IR ν_{max} 3401, 2947, 2909, 2830, 1591, 1481, 1454, 1431, 1210, 1137, 1030, 831, 796 cm^{-1}; MS (ESI, −ve) *m/z* 214 [(M − H)$^-$, 100%]; HRMS (M − H)$^-$ calcd for $C_{14}H_{16}NO$ 214.1232, found 214.1235.

*Glycozoline (**4**).* A magnetically stirred mixture of compound **21** (44 mg, 0.20 mmol) and 10 wt % Pd/C (44 mg) in diphenyl ether (5 mL) was stirred at 210 °C under an atmosphere of nitrogen for 0.33 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 5 mL). The combined filtrates were concentrated under reduced pressure, and the ensuing mixture of product **4** and diphenyl ether was then subjected to flash column chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 3/7 v/v ethyl acetate/40−60 petroleum ether), compound **4**[3a,15] (39 mg, 89%) as a white, crystalline solid, mp 180−181 °C (lit.[22b] mp. = 177−178 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.96 (broad s, 1H), 7.87 (s, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.36 (t, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.5 and 2.2 Hz, 1H), 3.88 (s, 3H), 2.47 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 154.5, 140.0, 136.1, 128.1, 127.7, 124.2(2), 124.2(0), 120.8, 115.6, 112.3, 111.5, 103.5, 56.1, 21.5; IR ν_{max} 3398, 2928, 1493, 1470, 1457, 1208, 1148, 1033, 806 cm^{-1}; MS (ESI, −ve) *m/z* 210 [(M − H)$^-$, 60%], 195 (100); HRMS (M − H)$^-$ calcd for $C_{14}H_{12}NO$ 210.0919, found 210.0912.

*4′-Methoxy-5-methyl-2′-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**23**).* A magnetically stirred mixture of commercially available 1-iodo-4-methoxy-2-nitrobenzene (**22**) (341 mg, 1.22 mmol), 2-iodo-4-methylcyclohex-2-en-1-one (**10**) (519 mg, 2.20 mmol), copper powder (311 mg, 4.89 g atom), CuI (349 mg, 1.83 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (100 mg, 0.12 mmol) in deoxygenated DMSO (24 mL) was heated to 50 °C under a nitrogen atmosphere for 6 h. The ensuing mixture was cooled to room temperature, quenched with water (10 mL), diluted with ethyl acetate (20 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 30 mL), and the separated organic phase associated with the filtrate was washed with water (2 × 50 mL) and brine (2 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 2/5/64 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), compound **23** (256 mg, 80%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.3 Hz, 1H), 7.15−7.09 (complex m, 2H), 6.75 (dd, *J* = 2.7 and 1.1 Hz, 1H), 3.85 (s, 3H), 2.75 (m, 1H), 2.65−2.40 (complex m, 2H), 2.19 (m, 1H), 1.80 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 159.7, 151.8, 149.2, 138.1, 132.7, 124.2, 119.7, 109.3, 56.0, 37.3, 31.8, 30.8, 20.5; IR ν_{max} 2960, 1681, 1529, 1353, 1302, 1266, 1236, 1032, 800 cm^{-1}; MS (ESI, +ve) *m/z* 284 [(M + Na)$^+$, 100%], 262 [(M + H)$^+$, 15]; HRMS (M + Na)$^+$ calcd for $C_{14}H_{15}NNaO_4$ 284.0899, found 284.0901.

*7-Methoxy-3-methyl-2,3,4,9-tetrahydro-1H-carbazole (**24**) and trans-4a-Hydroperoxy-7-methoxy-3-methyl-2,3,4,4a-tetrahydro-1H-carbazole (**25**).* A magnetically stirred mixture of compound **23** (202 mg, 0.77 mmol) and commercially available W-2 Raney nickel (404 mg, washed twice with absolute ethanol) in methanol (38 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 16 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 20 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/3/20 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether) afforded compound **24**[11a,14] (109 mg, 65%) as a white, crystalline solid, mp 130−132 °C: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.50 (broad s, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.63 (dd, *J* = 8.5 and 2.2 Hz, 1H), 3.76 (s, 3H), 2.83−2.71 (complex m, 3H), 2.19 (m, 1H), 1.90 (m, 2H), 1.50 (m, 1H), 1.11 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 156.6, 138.2, 133.4, 123.2, 118.5, 109.5, 108.6, 95.4, 55.7, 32.3, 30.6, 30.3, 23.5, 22.1; IR ν_{max} 3390, 2909, 2835, 1630, 1570, 1496, 1459, 1335, 1291, 1203, 1157, 1029, 826, 805 cm^{-1}; MS (ESI, +ve) *m/z* 238 [(M + Na)$^+$, 20%], 218 (100), 216 [(M + H)$^+$, 90]; HRMS (M + H)$^+$ calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1386.

Concentration of fraction B (R_f = 0.1 in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether) afforded hydroperoxide **25** (15 mg, 8%) as a white, crystalline solid, mp 106−108 °C: ^{1}H NMR [700 MHz, $(CD_3)_2CO$] δ δ 10.81 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.0 and 2.3 Hz, 1H), 3.82 (s, 3H), 2.82−2.76 (complex m, 1H), 2.68 (m, 1H), 2.43 (m, 1H), 2.14 (m, 2H), 1.13 (m, 1H), 0.95 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C

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NMR [175 MHz, $(CD_3)_2CO$] δ 186.1, 162.2, 157.4, 131.5, 123.8, 110.8, 107.4, 92.3, 55.8, 44.4, 37.4, 30.3, 28.1, 21.0; IR ν_{max} 3100, 2954, 2836, 1607, 1484, 1347, 1276, 1144, 1130, 1028, 845, 815 cm^{-1}; MS (ESI, +ve) m/z 270 [$(M + Na)^+$, 100%], 248 [$(M + H)^+$, 10]; HRMS (ESI) $(M + Na)^+$ calcd for $C_{14}H_{17}NNaO_3$ 270.1106, found 270.1107.

*2-Methoxy-6-methyl-9H-carbazole (**26**).* A magnetically stirred mixture of compound **24** (100 mg, 0.46 mmol) and 10 wt % Pd/C (100 mg) in diphenyl ether (10 mL) was stirred at 210 °C under an atmosphere of nitrogen for 0.5 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated under reduced pressure, and the ensuing mixture of product **26**[9c,h,22d,23a,b] and diphenyl ether was then subjected to flash column chromatography (silica, 2/5/60 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), compound **26** (87 mg, 88%) as a white solid, mp 229−231 °C (lit.[9c] mp 228−229 °C): ^1H NMR [400 MHz, $(CD_3)_2CO$] δ 10.03 (braod s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.78 (s, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.77 (dd, J = 8.6 and 2.2 Hz, 1H), 3.85 (s, 3H), 2.46 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 160.0, 142.7, 139.3, 128.6, 126.3, 124.4, 121.5, 120.0, 117.6, 111.1, 108.6, 95.3, 55.7, 21.5; IR ν_{max} 3391, 2962, 1615, 1460, 1310, 1261, 1164, 1035, 811 cm^{-1}; MS (ESI, +ve) m/z 212 [$(M + H)^+$, 100%]; HRMS $(M + H)^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1077.

*Clauszoline K (**5**).* A magnetically stirred solution of 2-methoxy-6-methyl-9*H*-carbazole (**26**) (50 mg, 0.24 mmol) in methanol/water (16 mL of 10/1 v/v mixture) was treated with DDQ (226 mg, 0.99 mmol). The ensuing mixture was stirred at room temperature for 4 h and then diluted with ethyl acetate (30 mL). The separated organic phase was washed with $NaHCO_3$ (2 × 15 mL of a saturated aqueous solution), water (1 × 30 mL), and brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1/3 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1/1 v/v ethyl acetate/40−60 petroleum ether), compound **5** (35 mg, 66%) as a yellow solid, mp 170−171 °C (lit.[22d] mp 184−185 °C): ^1H NMR [400 MHz, $(CD_3)_2CO$] δ 10.72 (broad s, 1H), 10.07 (s, 1H), 8.58 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.88 (broadened d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.3 Hz, 1H), 6.91 (dd, J = 8.6 and 2.3 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 192.0, 160.8, 144.8, 143.1, 130.1, 126.3, 124.4, 123.5, 122.2, 117.6, 111.8, 110.1, 96.0, 55.8; IR ν_{max} 3306, 2923, 2849, 1667, 1604, 1569, 1456, 1317, 1159, 817, 807 cm^{-1}; MS (ESI, −ve) m/z 224 [$(M - H)^-$, 100%], 209 (54); HRMS $(M - H)^-$ calcd for $C_{14}H_{10}NO_2$ 224.0712, found 224.0705.

*Methyl 3-Bromo-5-methoxy-4-nitrobenzoate (**27**). Step i.* A magnetically stirred and ice-cold solution of methyl 4-amino-3-methoxybenzoate (3.00 mg, 16.56 mmol) in chloroform (33 mL) was treated, in portions over 1 h, with *N*-bromosuccinimide (NBS) (2.95, 16.6 mmol). The ensuing mixture was stirred at 5−10 °C for 2 h before being diluted with dichloromethane (1 × 200 mL) then washed with $Na_2S_2O_3$ (2 × 100 mL of a 20% w/v aqueous solution), water (2 × 100 mL), and brine (1 × 100 mL). The separated organic phase was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3/17 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1/3 v/v ethyl acetate/40−60 petroleum ether), methyl 4-amino-3-bromo-5-methoxybenzoate[25] (3.70 g, 86%) as a yellow solid, mp 90−91 °C: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.38 (s, 1H), 4.65 (broad s, 2H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 146.3, 139.4, 127.1, 119.5, 109.9, 106.8, 56.2, 52.1; IR ν_{max} 3503, 3399, 1692, 1603, 1566, 1502, 1435, 1270, 1209, 1041, 995, 759 cm^{-1}; MS (EI, 70 eV) m/z 261 and 259 ($M^{+\bullet}$, 98 and 100%, respectively), 246 and 244 (both 65 and 63, respectively), 230 and 228 (both 54); HRMS $M^{+\bullet}$ calcd for $C_9H_{10}{}^{79}BrNO_3$ 258.9844, found 258.9846.

Step ii. A magnetically stirred solution of methyl 4-amino-3-bromo-5-methoxybenzoate (4.24 g, 16.31 mmol), obtained as described immediately above, in 1,2-dichloroethane (163 mL) was treated with *m*-chloroperbenzoic acid (*m*CPBA) (11.26 g of ca. 77% technical grade material, 65.3 mmol). The resulting mixture was heated to 70 °C for 14 h before being cooled, diluted with dichloromethane (150 mL), washed with NaOH (2 × 150 mL of a 1 M aqueous solution) followed by brine (1 × 100 mL), and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1/8 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1/2 v/v ethyl acetate/40−60 petroleum ether), methyl 3-bromo-5-methoxy-4-nitrobenzoate (**27**) (4.13 g, 87%) as a yellow solid, mp 103−104 °C: ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 1.4 Hz, 1H), 7.65 (d, J = 1.4 Hz, 1H), 3.95(9) (s, 3H), 3.95(6) (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 151.8, 144.7, 133.1, 126.2, 113.8, 112.8, 57.1, 53.2; IR ν_{max} 3097, 1730, 1540, 1406, 1289, 1248, 1037, 984, 822, 764 cm^{-1}; MS (EI, 70 eV) m/z 291 and 289 ($M^{+\bullet}$, 98 and 100%, respectively) 259 and 257 (40 and 35, respectively) 199 and 197 (60 and 50, respectively); HRMS $M^{+\bullet}$ calcd for $C_9H_8{}^{79}BrNO_5$ 288.9586, found 288.9587.

*Methyl 5-Methoxy-6-nitro-2′-oxo-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-3-carboxylate (**28**).* A magnetically stirred mixture of methyl 3-bromo-5-methoxy-4-nitrobenzoate (**28**) (2.56 g, 8.82 mmol), 2-iodocyclohex-2-en-1-one (**9**) (890 mg, 4.01 mmol), copper powder (1.27 g, 20.04 g atom), CuI (1.15 g, 6.01 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (164 mg, 0.20 mmol) in deoxygenated DMSO (17 mL) was heated to 50 °C under a nitrogen atmosphere for 28 h. The reaction mixture was then cooled to room temperature, quenched with water (20 mL), diluted with ethyl acetate (40 mL) and filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 60 mL), and the organic phase associated with the filtrate was washed with water (2 × 100 mL) and then brine (2 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.5 in 1/1 v/v ethyl acetate/40−60 petroleum ether), compound **28** (478 mg, 39%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz, 1H), 7.05 (t, J = 4.2 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.58−2.50 (complex m, 4H), 2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 165.4, 151.2, 150.2, 143.3, 136.3, 132.4, 131.6, 124.2, 113.3, 57.0, 52.9, 38.3, 26.5, 22.7; IR ν_{max} 2956, 2924, 1716, 1683, 1535, 1360, 1245, 1022, 838, 766 cm^{-1}; MS (ESI, +ve) m/z 328 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{15}H_{15}NNaO_6$ 328.0797, found 328.0793.

*Methyl 8-Methoxy-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate (**29**).* A magnetically stirred mixture of compound **28** (400 mg, 1.31 mmol) and commercially available W-2 Raney nickel (800 mg, washed twice with absolute ethanol) in methanol (65 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 16 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 40 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 3/17 v/v ethyl acetate/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 1/2 v/v ethyl acetate/40−60 petroleum ether), compound **29** (268 mg, 79%) as a white solid, mp 181−182 °C: ^1H NMR [400 MHz, $(CD_3)_2CO$] δ 10.15 (broad s, 1H), 7.81 (s, 1H), 7.25 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.77 (m, 2H), 2.70 (m, 2H), 1.92−1.82 (complex m, 4H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 168.5, 146.2, 136.6, 129.7, 129.4, 122.1, 114.8, 111.7, 102.5, 55.7, 51.8, 24.0, 23.9, 23.7, 21.6; IR ν_{max} 3339, 2928, 2836, 1696, 1628, 1366, 1326, 1231, 1188, 993, 765 cm^{-1}; MS (ESI, +ve) m/z 541 (65%), 282

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[(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{15}H_{17}NNaO_3$ 282.1106, found 282.1105.

*Mukonine (**6**).* A magnetically stirred mixture of compound **29** (264 mg, 1.02 mmol) and 10 wt % Pd/C (264 mg) in mesitylene (20 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 20 mL). The filtrate was concentrated under reduced pressure and the ensuing mixture of product **6** and mesitylene then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1/3 v/v ethyl acetate/40−60 petroleum ether), compound **6**[17] (171 mg, 66%) as a white solid, mp 196−198 °C (lit.[17a] mp 193−195 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (broad s, 1H), 8.48 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.49−7.43 (complex m, 2H), 7.28 (m, 1H), 4.05 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.2, 139.6, 133.0, 126.5, 123.9, 123.7, 122.0, 120.9, 120.4, 116.4, 111.4, 106.8, 55.9, 52.2; IR ν_{max} 3350, 2941, 1689, 1608, 1585, 1433, 1338, 1255, 758, 732 cm^{-1}; MS (ESI, +ve) m/z 533 (28%), 278 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{15}H_{13}NNaO_3$ 278.0793, found 278.0792.

*6-Methyl-9H-carbazol-2-ol (**30**).* A magnetically stirred solution of compound **26** (50 mg, 0.24 mmol) in dichloromethane (15 mL) maintained at −78 °C under an atmosphere of nitrogen was treated, dropwise, with BBr_3 (470 μL of a 1 M solution in dichloromethane, 0.47 mmol). The resulting mixture was stirred at −78 °C for another 2 h and then warmed to −40 °C. After 2 h the reaction mixture was recooled to −78 °C and a further portion of BBr_3 (520 μL of a 1 M solution in dichloromethane, 0.52 mmol) added dropwise. The reaction mixture was then warmed to 22 °C, stirred at this temperature for 11 h, cooled to 0 °C, and then quenched by the slow addition of $NaHCO_3$ (30 mL of a saturated aqueous solution). The resulting mixture was extracted with dichloromethane (1 × 20 mL), and the combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3/17 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions [R_f = 0.2(5) in 3/7 v/v ethyl acetate/40−60 petroleum ether], compound **30**[9h] (39 mg, 84%) as a white, crystalline solid, mp 259−261 °C (lit.[9h] mp 230−233 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.91 (broad s, 1H), 8.25 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 8.4 and 2.1 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 157.4, 143.0, 139.2, 128.4, 126.0, 124.7, 121.5, 119.8, 117.1, 110.9, 109.1, 97.4, 21.5; IR ν_{max} 3403, 2922, 2853, 1633, 1616, 1490, 1459, 1296, 1026, 804 cm^{-1}; MS (ESI, −ve) m/z 196 [(M − H)$^-$, 100%]; HRMS (M − H)$^-$ calcd for $C_{13}H_{10}NO$ 196.0762, found 196.0767.

*Karapinchamine A (**7**).* A magnetically stirred solution of compound **30** (27 mg, 0.14 mmol) in anhydrous THF (7 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise, with *n*-BuLi (340 μL of a 1.6 M solution in *n*-hexane, 0.55 mmol). After 0.17 h, a solution of geranyl bromide (51 mg, 0.21 mmol) in THF (7 mL) was added dropwise over 0.5 h. The resulting mixture was warmed to 22 °C, stirred at this temperature for 1.5 h, then cooled to 0 °C and quenched with NH_4Cl (15 mL of a saturated aqueous solution). The resulting mixture was extracted with ethyl acetate (2 × 30 mL), and the combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1/9 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 3/7 v/v ethyl acetate/40−60 petroleum ether), compound **7**[7e,18] (23 mg, 50%) as a white solid, mp 118−119 °C (lit.[7e] mp 124.3−125.6 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.23−7.18 (complex m, 2H), 6.78 (d, J = 1.9 Hz, 1H), 6.70 (dd, J = 8.3 and 2.0 Hz, 1H), 5.24 (m, 1H), 5.02 (m, 1H), 4.88 (s, 1H), 4.79 (d, J = 6.1 Hz, 2H), 2.52 (s, 3H), 2.09−1.98 (complex m, 4H), 1.90 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.2, 138.9, 138.7, 131.9, 128.4, 125.8, 123.9, 123.4, 121.2, 120.0, 119.6, 117.1, 108.4, 107.7, 95.2, 41.3, 39.5, 26.4, 25.8, 21.5, 17.8, 16.8; IR ν_{max} 3278, 2922, 2855, 1635, 1610, 1487, 1471, 1348, 1171, 801 cm^{-1}; MS (ESI, +ve) m/z 356 [(M + Na)$^+$, 100%], 334 [(M + H)$^+$, 20]; HRMS (M + Na)$^+$ calcd for $C_{23}H_{27}NNaO$ 356.1990, found 356.1994.

*4′-Methoxy-2′-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (**31**).* A magnetically stirred mixture of 1-iodo-4-methoxy-2-nitrobenzene (**22**) (912 mg, 3.27 mmol), 2-iodocyclohex-2-en-1-one (**9**) (330 mg, 1.49 mmol), copper powder (472 mg, 7.43 g atom), CuI (425 mg, 2.23 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (61 mg, 0.07 mmol) in deoxygenated DMSO (15 mL) was heated to 50 °C under a nitrogen atmosphere for 10 h. The reaction mixture was then cooled to room temperature, quenched with water (15 mL), diluted with ethyl acetate (30 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 40 mL), and the separated organic phase associated with the filtrate was washed with water (2 × 80 mL) and brine (2 × 80 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 2/5/44 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.3 in 2/5/11 v/v/v ethyl acetate/dichloromethane/40−60 petroleum ether), compound **31**[10,11b] (334 mg, 91%) as a light yellow oil: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.51 (d, J = 2.2 Hz, 1H), 7.28 (m, 2H), 7.10 (m, 1H), 3.92 (s, 3H), 2.58 (m, 2H), 2.46 (m, 2H), 2.09 (m, 2H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 196.5, 160.5, 150.4, 147.5, 139.5, 133.6, 125.1, 120.0, 109.9, 56.4, 39.0, 27.0, 23.5; IR ν_{max} 2945, 1678, 1525, 1496, 1353, 1232, 1035, 913, 830, 798 cm^{-1}; MS (ESI, +ve) m/z 270 [(M + Na)$^+$, 100%], 248 [(M + H)$^+$, 10]; HRMS (M + Na)$^+$ calcd for $C_{13}H_{13}NNaO_4$ 270.0742, found 270.0739.

*7-Methoxy-2,3,4,9-tetrahydro-1H-carbazole (**32**).* A magnetically stirred mixture of compound **31** (100 mg, 0.40 mmol) and commercially available W-2 Raney nickel (200 mg, washed twice with absolute ethanol) in methanol (23 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 16 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 20 mL) (*Caution! After these washings water should be added to the residual solid so as to prevent a fire.*). The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 1/3/20 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.4(5) in 1/3/6 v/v/v acetone/dichloromethane/40−60 petroleum ether), compound **32**[10,11b,26] (62 mg, 76%) as a white, crystalline solid, mp 138−139 °C (lit.[10] mp 136−142 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (broad s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.75 (dd, J = 8.5 and 2.2 Hz, 1H), 3.84 (s, 3H), 2.69 (m, 4H), 1.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 136.5, 132.9, 122.5, 118.3, 110.1, 108.4, 95.0, 56.0, 23.4, 23.3(5), 23.3(4), 21.1; IR ν_{max} 3405, 2919, 2842, 1628, 1464, 1307, 1213, 1156, 1029, 826, 803 cm^{-1}; MS (ESI, +ve) m/z 202 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1230.

*2-Methoxy-9H-carbazole (**8**).* A magnetically stirred mixture of compound **32** (40 mg, 0.20 mmol) and 10 wt % Pd/C (40 mg) in mesitylene (5 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated under reduced pressure, and the ensuing mixture of product **6** and mesitylene was then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.3 in 1/5 v/v ethyl acetate/40−60 petroleum ether), compound **8**[6f,k,l,9j] (25 mg, 64%) as a white, crystalline solid, mp 227−228 °C (lit.[6f] mp 233−235 °C): ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 10.18 (broad s, 1H), 7.97 (m, 2H), 7.44 (d,

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J = 8.1 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.13 (m, 1H), 7.03 (broad s, 1H), 6.80 (m, 1H), 3.86 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 160.1, 142.4, 141.0, 125.0, 124.2, 121.6, 120.0, 119.7, 117.7, 111.4, 108.8, 95.4, 55.7; IR ν_{max} 3391, 2929, 1608, 1463, 1444, 1308, 1196, 1163, 1033, 818, 727 cm^{-1}; MS (ESI, −ve) m/z 196 [$(M - H)^-$, 100%]; HRMS $(M - H)^-$ calcd for $C_{13}H_{10}NO$ 196.0762, found 196.0753.

X-ray Crystallographic Studies. *Crystallographic Data. Compound 1:* $C_{12}H_9N$, M_r = 167.21, T = 150 K, orthorhombic, space group *Pnma*, Z = 4, a = 7.6589(2) Å, b = 19.0353(5) Å, c = 5.6814(1) Å; V = 828.29(3) Å^3, D_x = 1.341 g cm^{-3}, 864 unique data ($2\theta_{max}$ = 147.4°), R = 0.035 [for 795 reflections with $I > 2.0\sigma(I)$]; R_w = 0.058 (all data), S = 1.00.

Compound 2: $C_{13}H_{11}N$, M_r = 181.24, T = 150 K, monoclinic, space group $P2_1/c$, Z = 4, a = 20.3990(8) Å, b = 5.7846(2) Å, c = 7.8899(3) Å; β = 98.458(4)°; V = 920.88(6) Å^3, D_x = 1.307 g cm^{-3}, 1858 unique data ($2\theta_{max}$ = 147.8°), R = 0.057 [for 1748 reflections with $I > 2.0\sigma(I)$]; R_w = 0.096 (all data), S = 1.00.

Compound 3: $C_{14}H_{13}NO$, M_r = 211.26, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 11.4714(17) Å, b = 5.6130(6) Å, c = 16.915(2) Å; β = 95.648(12)°; V = 1083.9(2) Å^3, D_x = 1.295 g cm^{-3}, 2160 unique data ($2\theta_{max}$ = 151.8°), R = 0.058 [for 1763 reflections with $I > 2.0\sigma(I)$]; R_w = 0.164 (all data), S = 1.00.

Compound 4: $C_{14}H_{13}NO$, M_r = 211.26, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.4420(1) Å, b = 7.5921(1) Å, c = 21.9422(3) Å; V = 1073.16(3) Å^3, D_x = 1.308 g cm^{-3}, 2166 unique data ($2\theta_{max}$ = 147.8°), R = 0.035 [for 2114 reflections with $I > 2.0\sigma(I)$]; R_w = 0.064 (all data), S = 1.00.

Compound 5: $C_{14}H_{11}NO_2$, M_r = 225.25, T = 150 K, orthorhombic, space group *Pbca*, Z = 8, a = 7.1367(1) Å, b = 13.2390(1) Å, c = 22.5108(2) Å; V = 2126.88(4) Å^3, D_x = 1.407 g cm^{-3}, 2152 unique data ($2\theta_{max}$ = 147.8°), R = 0.033 [for 2089 reflections with $I > 2.0\sigma(I)$]; R_w = 0.058 (all data), S = 1.00.

Compound 6: $C_{15}H_{13}NO_3$, M_r = 255.27, T = 150 K, monoclinic, space group $C2/c$, Z = 8, a = 15.7767(2) Å, b = 9.4629(1) Å, c = 16.1402(2) Å; β = 91.7342(13)°; V = 2408.52(5) Å^3, D_x = 1.408 g cm^{-3}, 3284 unique data ($2\theta_{max}$ = 59.6°), R = 0.039 [for 2869 reflections with $I > 2.0\sigma(I)$]; R_w = 0.077 (all data), S = 1.00.

Compound 17: $C_{14}H_{15}NO_4$, M_r = 261.27, T = 150 K, monoclinic, space group $P2_1/c$, Z = 8, a = 21.5986(4) Å, b = 6.89910(11) Å, c = 17.6362(3) Å; β = 104.596(2)°; V = 2543.16(8) Å^3, D_x = 1.365 g cm^{-3}, 5147 unique data ($2\theta_{max}$ = 147.6°), R = 0.084 [for 4826 reflections with $I > 2.0\sigma(I)$]; R_w = 0.214 (all data), S = 1.12.

Compound 25: $C_{14}H_{17}NO_3$, M_r = 247.29, T = 150 K, monoclinic, space group $P2_1/c$, Z = 4, a = 14.6135(2) Å, b = 5.8504(1) Å, c = 14.6942 (2) Å; β = 96.2796(15)°; V = 1248.74(3) Å^3, D_x = 1.315 g cm^{-3}, 2542 unique data ($2\theta_{max}$ = 147.6°), R = 0.036 [for 2433 reflections with $I > 2.0\sigma(I)$]; R_w = 0.098 (all data), S = 1.00.

Structure Determination. The image for compound **6** was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) fitted with an area detector, and the data were extracted using the DENZO/Scalepack package.[34] Images for compounds **1**−**5**, **17**, and **25** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[35] The structure solutions for all eight compounds were solved by direct methods (SIR92)[36] then refined using the CRYSTALS program package.[37] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1525166, 1525163, 1525164, 1525162, 1525167, 1525160, 1525161, and 1525165 for compounds **1**−**6**, **17**, and **25**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: + 44 1223 336033). Single-crystal X-ray analyses of compound **1** have been reported previously.[38]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00044.

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
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Crystallographic data (CIF)
Crystallographic data and anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds **1**−**6**, **17**, and **25**, ^{1}H and ^{13}C NMR spectra of compounds **1**−**15**, **17**, **18**, **20**, **21**, **23**−**32**, and methyl 4-amino-3-bromo-5-methoxybenzoate (precursor to compound **27**) (PDF)

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

A Palladium-catalyzed Ullmann Cross-coupling/Reductive Cyclisation Route to the Carbazole Natural Products 3-Methyl-9*H*-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine and Karapinchamine A

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Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

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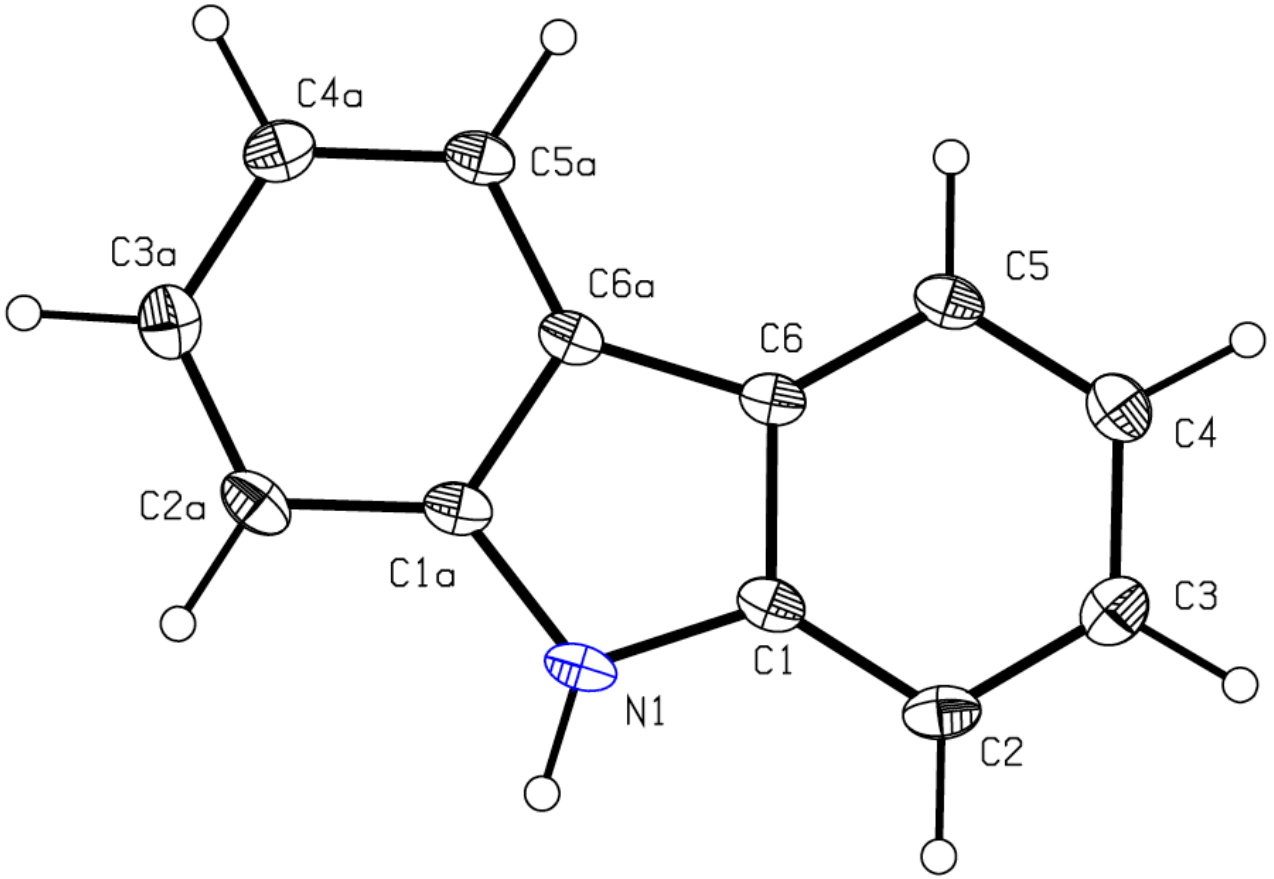


Figure S1: Structure of compound **1** (CCDC 1525166) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

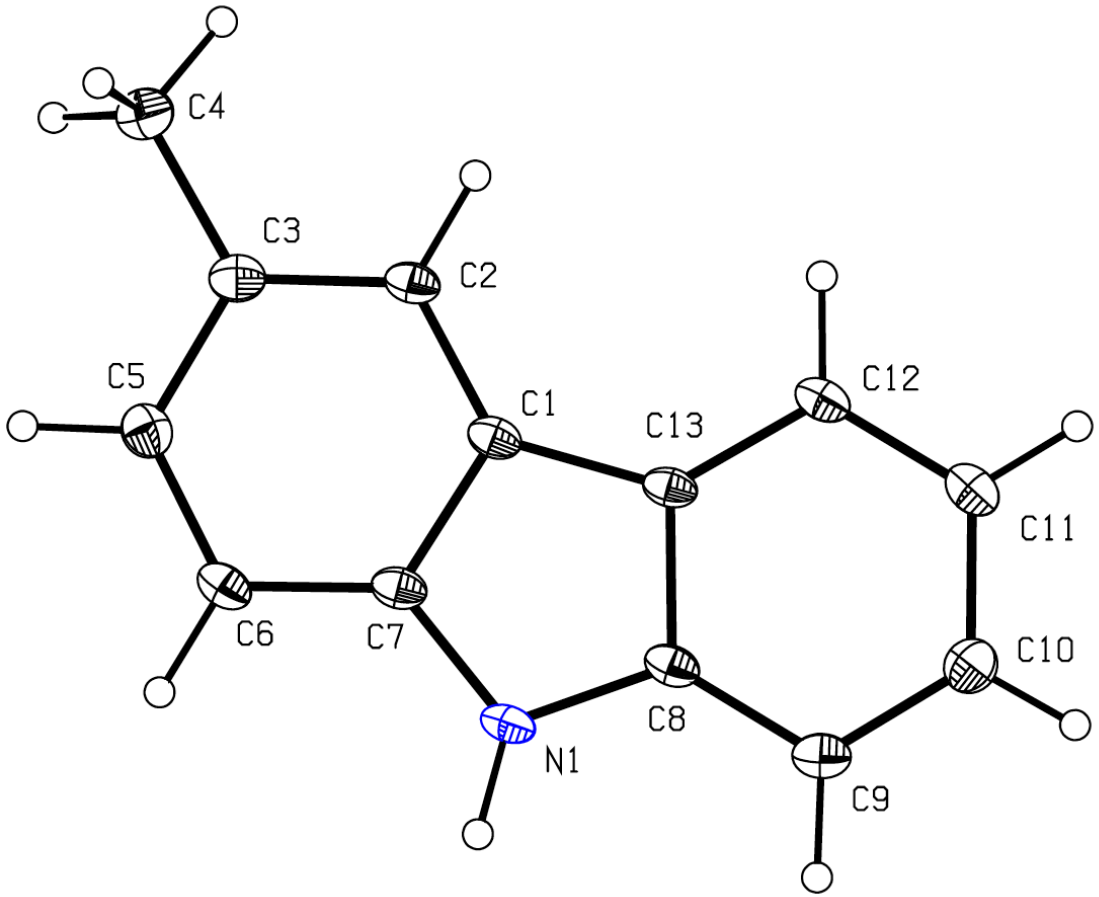


Figure S2: Structure of compound **2** (CCDC 1525163) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

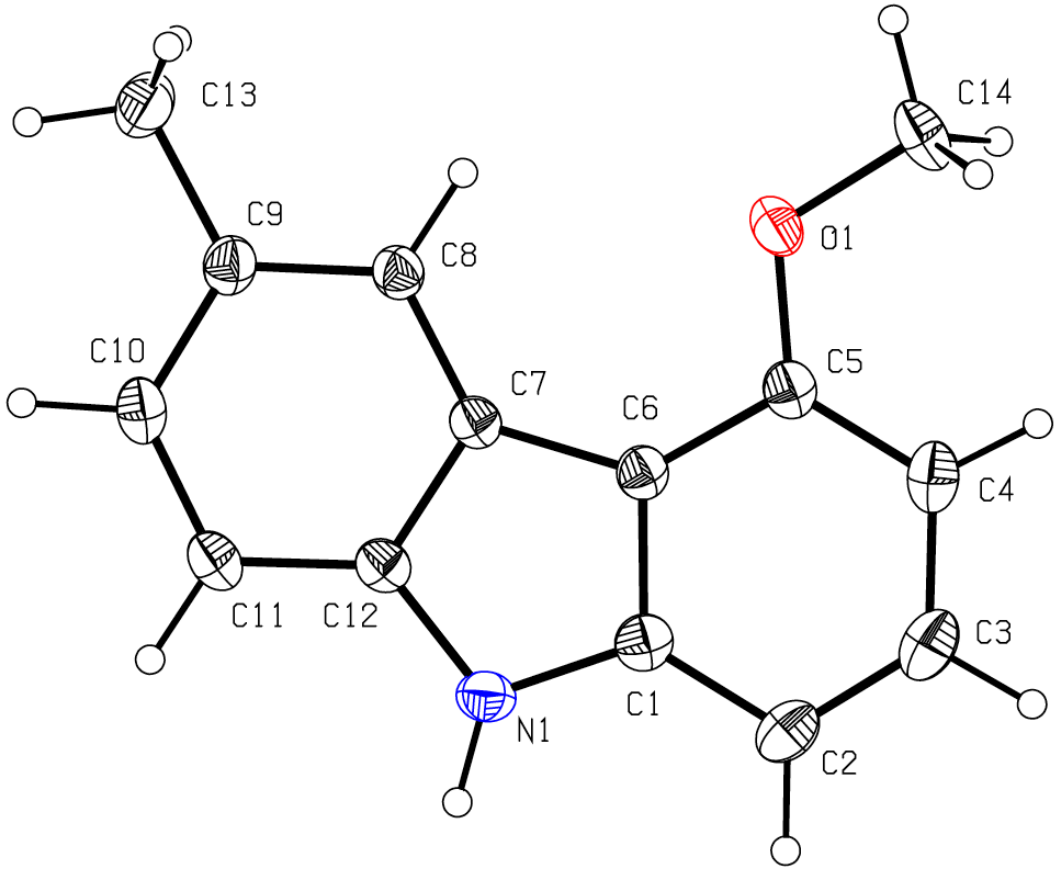


Figure S3: Structure of compound **3** (CCDC 1525164) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

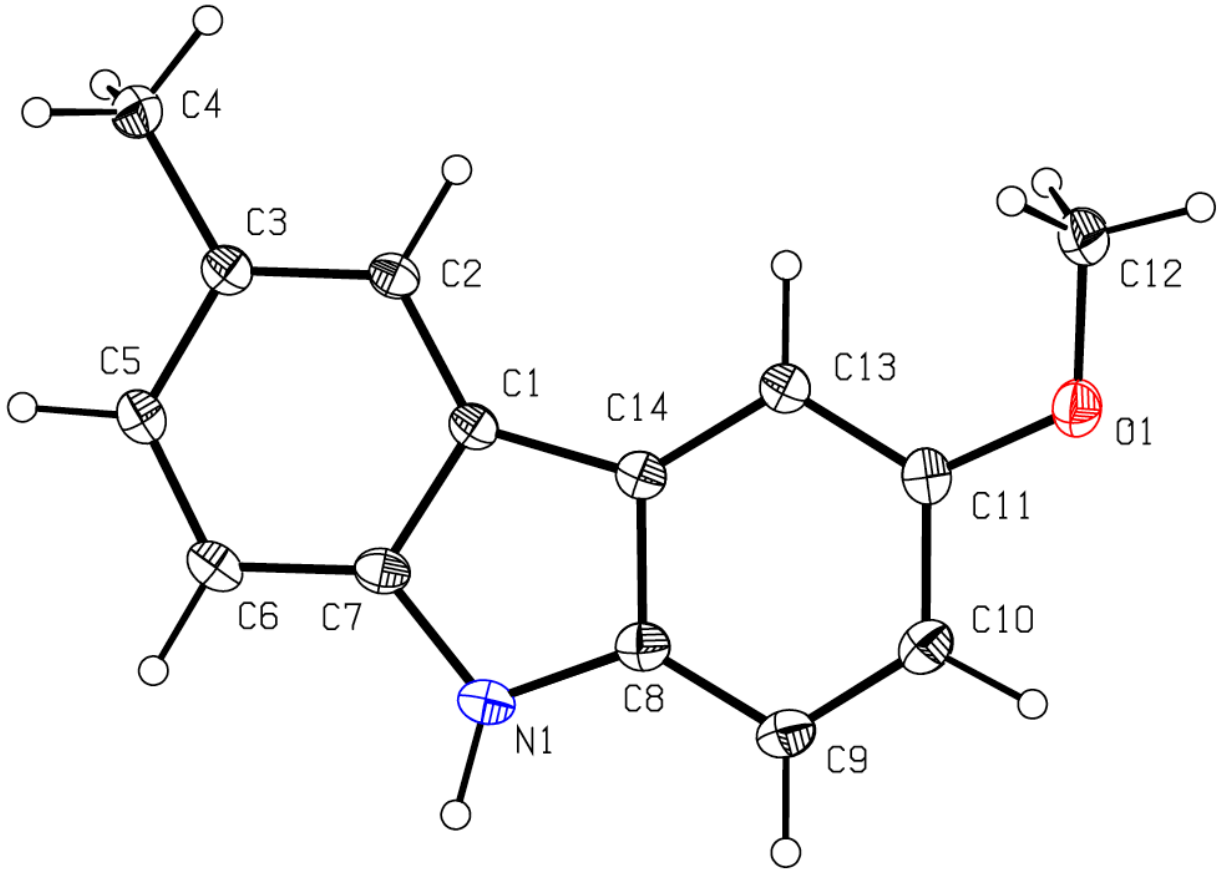


Figure S4: Structure of compound **4** (CCDC 1525162) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

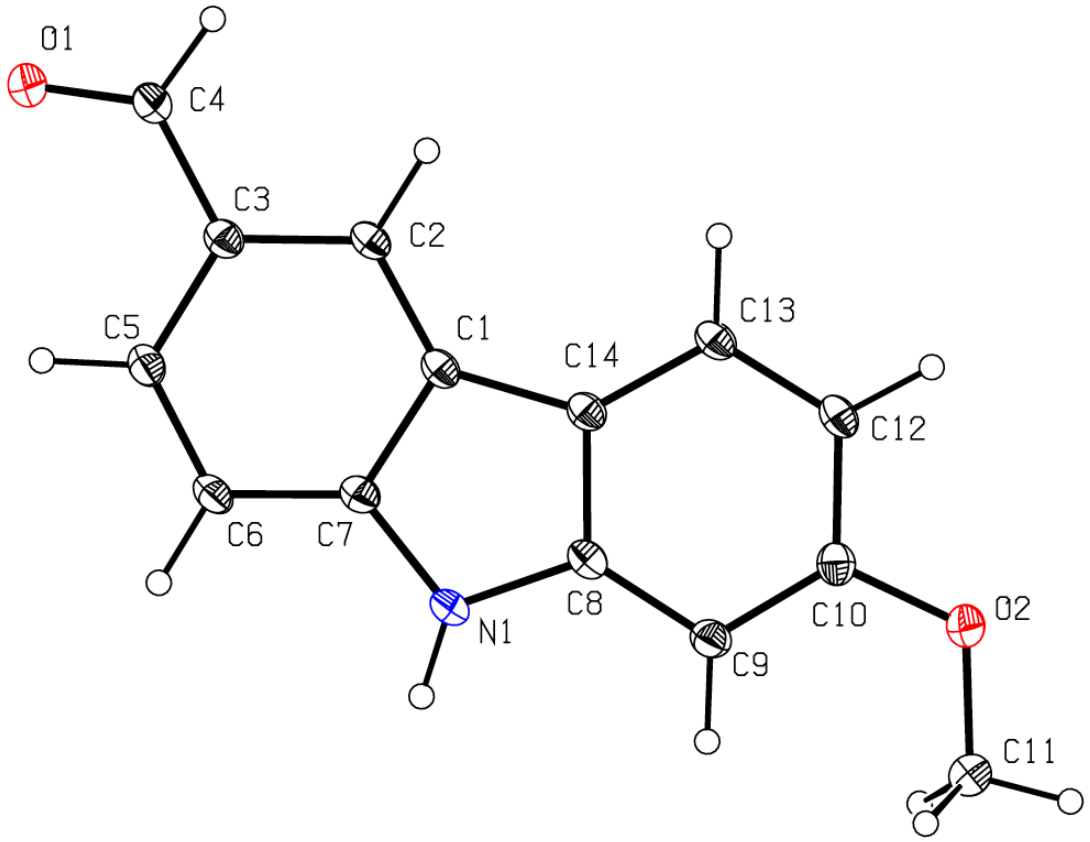


Figure S5: Structure of compound **5** (CCDC 1525167) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

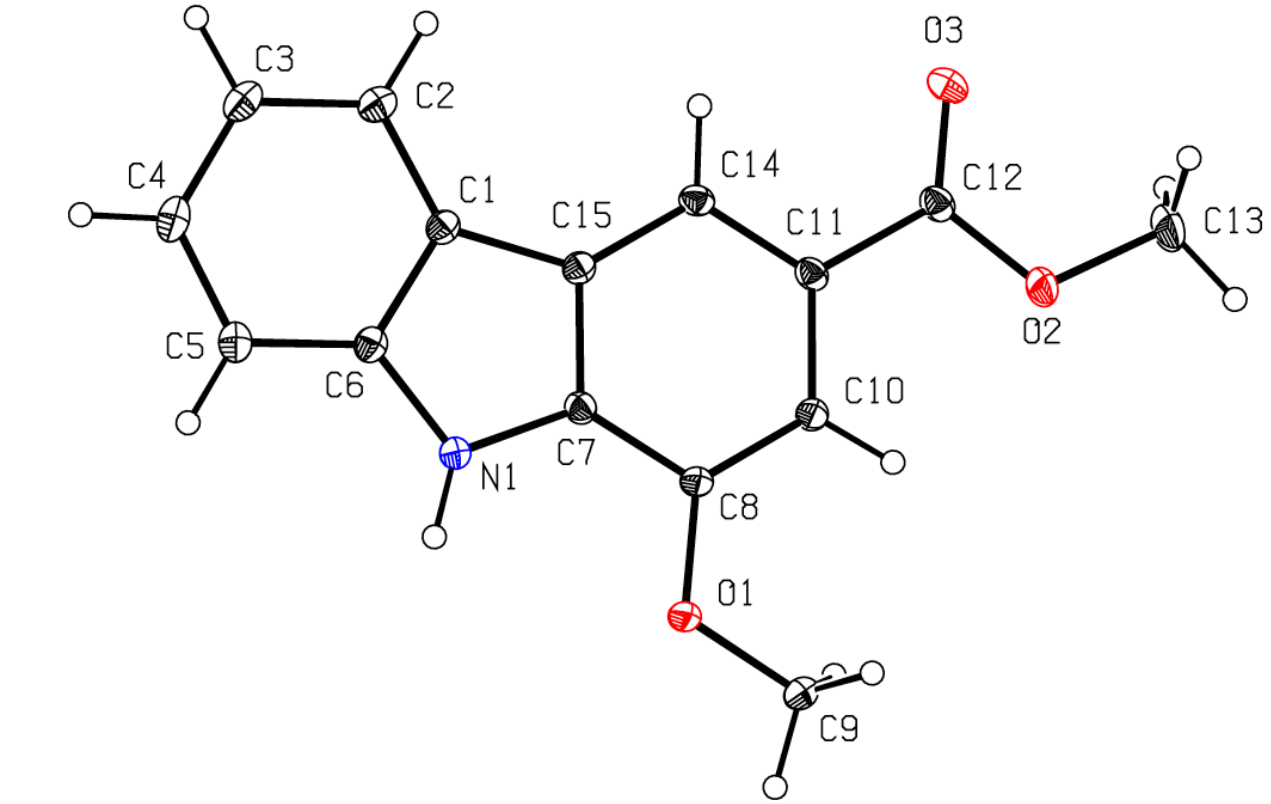


Figure S6: Structure of compound **6** (CCDC 1525160) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

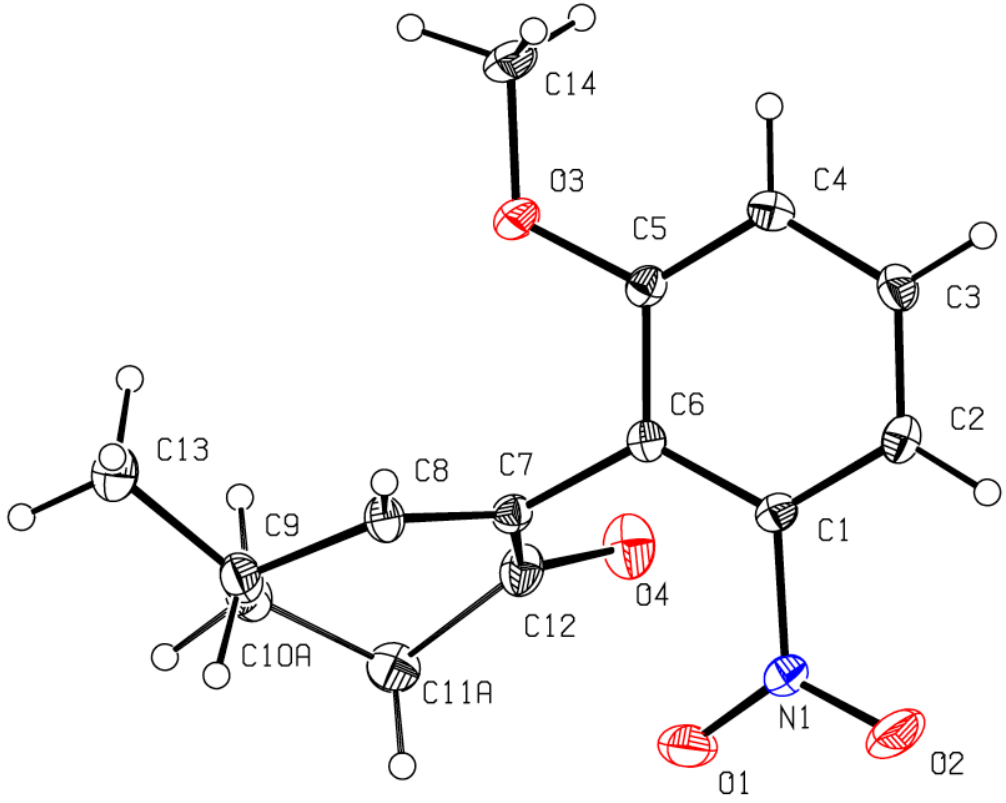


Figure S7: Structure of compound **17** (CCDC 1525161) with labeling of selected atoms. Only one of the two molecules present in the asymmetric unit is shown. There was some disordering of atoms C10A and C11A - only the major conformer is shown. This conformer had an occupancy of 81.6%. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

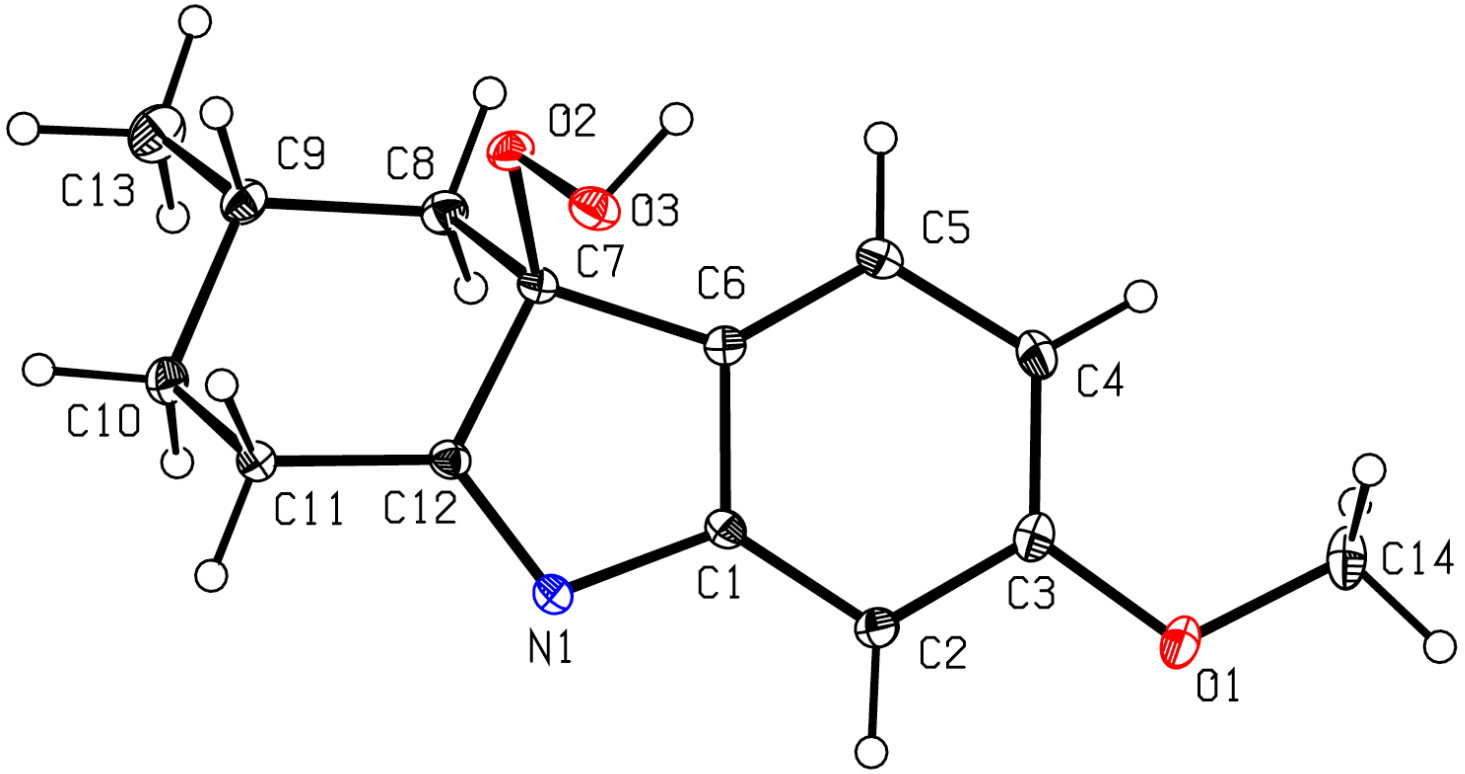


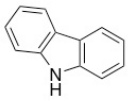
Figure S8: Structure of compound **25** (CCDC 1525165) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

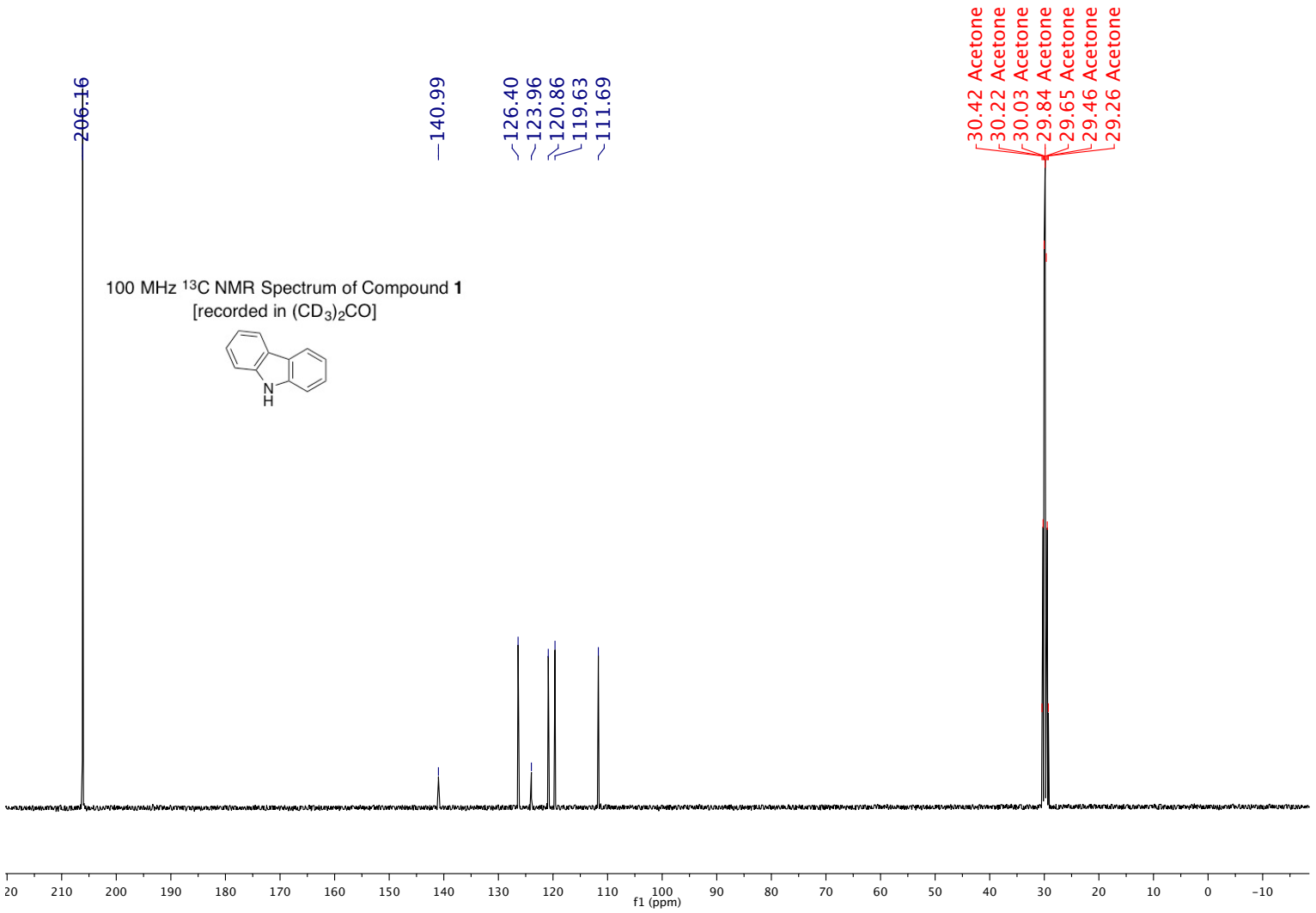
Table S1: *Comparison of the ^{13}C NMR Spectral Data Reported by Yoshikawa[18] and Ma[7e] for Karapinchamine A with the Equivalent Data Recorded for Compound 7 Prepared by the Present Route*

δ_C (*ex*. Yoshikawa)[a]	δ_C (*ex*. Ma)[b]	δ_C (*ex*. Present Route)[c]	**Δδ** δ_C(PR[d]) – δ_C(Y'kawa)
154.5	154.2	154.6	0.1
142.0	141.9	142.2	0.2
138.8	138.7	138.9	0.1
138.5	138.4	138.7	0.2
131.8	131.7	131.9	0.1
128.3	128.1	128.4	0.1
125.6	125.5	125.8	0.2
123.7	123.7	123.9	0.2
123.3	123.1	123.4	0.1
121.0	121.0	121.2	0.2
119.8	119.6	120.0	0.2
119.5	119.4	119.6	0.1
117.0	116.8	117.1	0.1
108.3	108.3	108.4	0.1
107.5	107.5	107.7	0.2
95.1	95.1	95.2	0.1
41.2	40.9	41.3	0.1
39.4	39.3	39.5	0.1
27.2	26.2	26.4	0.2
25.5	25.5	25.8	0.3
21.4	21.3	21.5	0.1
17.7	17.6	17.8	0.1
16.6	16.4	16.8	0.2

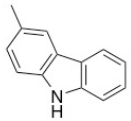
[a] Spectrum recorded in $CDCl_3$ at 125 or 150 MHz; [b] Spectrum recorded in $CDCl_3$ at 75 MHz; [c] Spectrum recorded in $CDCl_3$ at 100 MHz; [d] PR = present route.

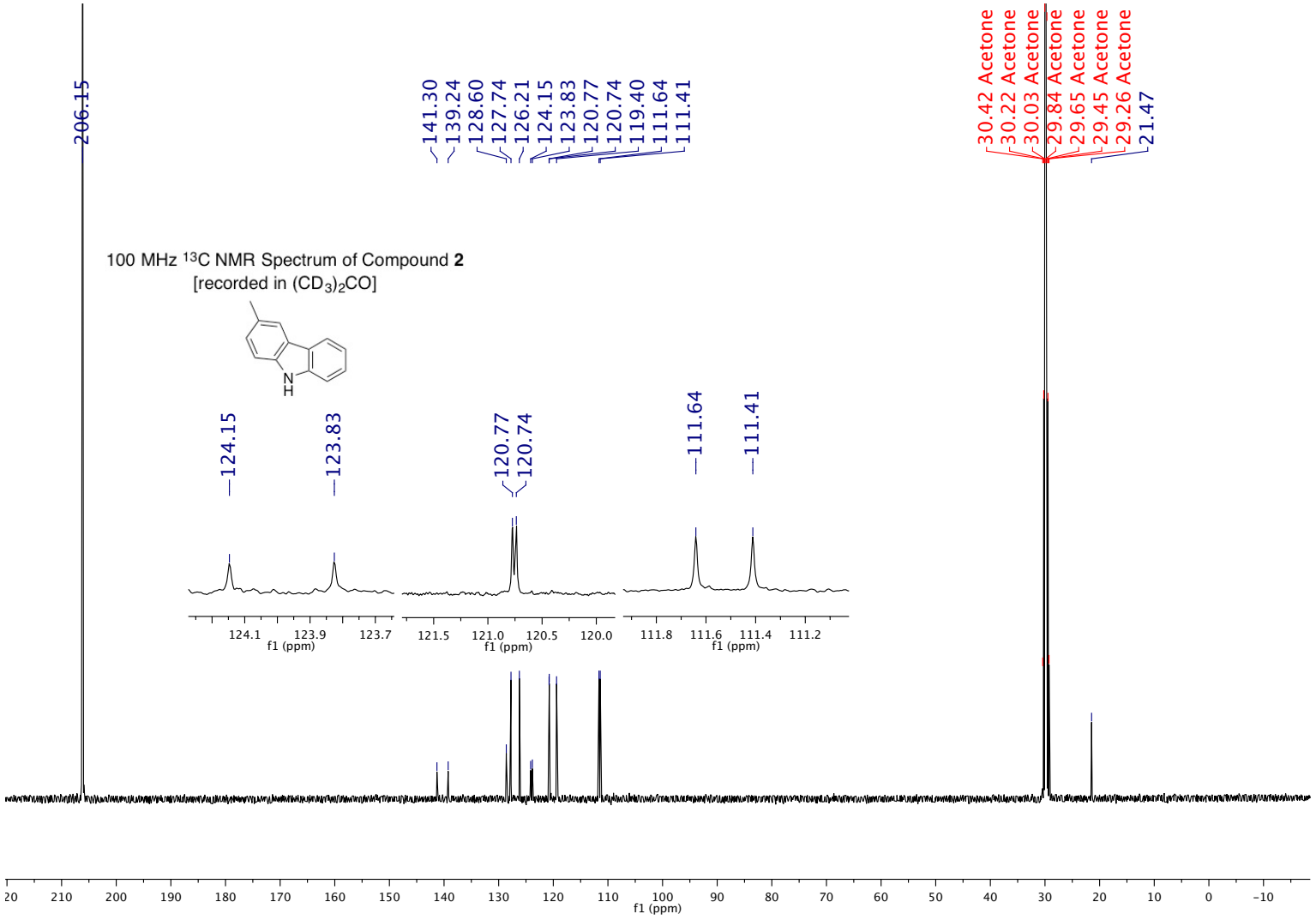
400 MHz ^{1}H NMR Spectrum of Compound **1**
[recorded in $(CD_3)_2CO$]



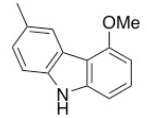

206.16
140.99
126.40
123.96
120.86
119.63
111.69
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
100 MHz ^{13}C NMR Spectrum of Compound **1**
[recorded in $(CD_3)_2CO$]
N
H
f1 (ppm)

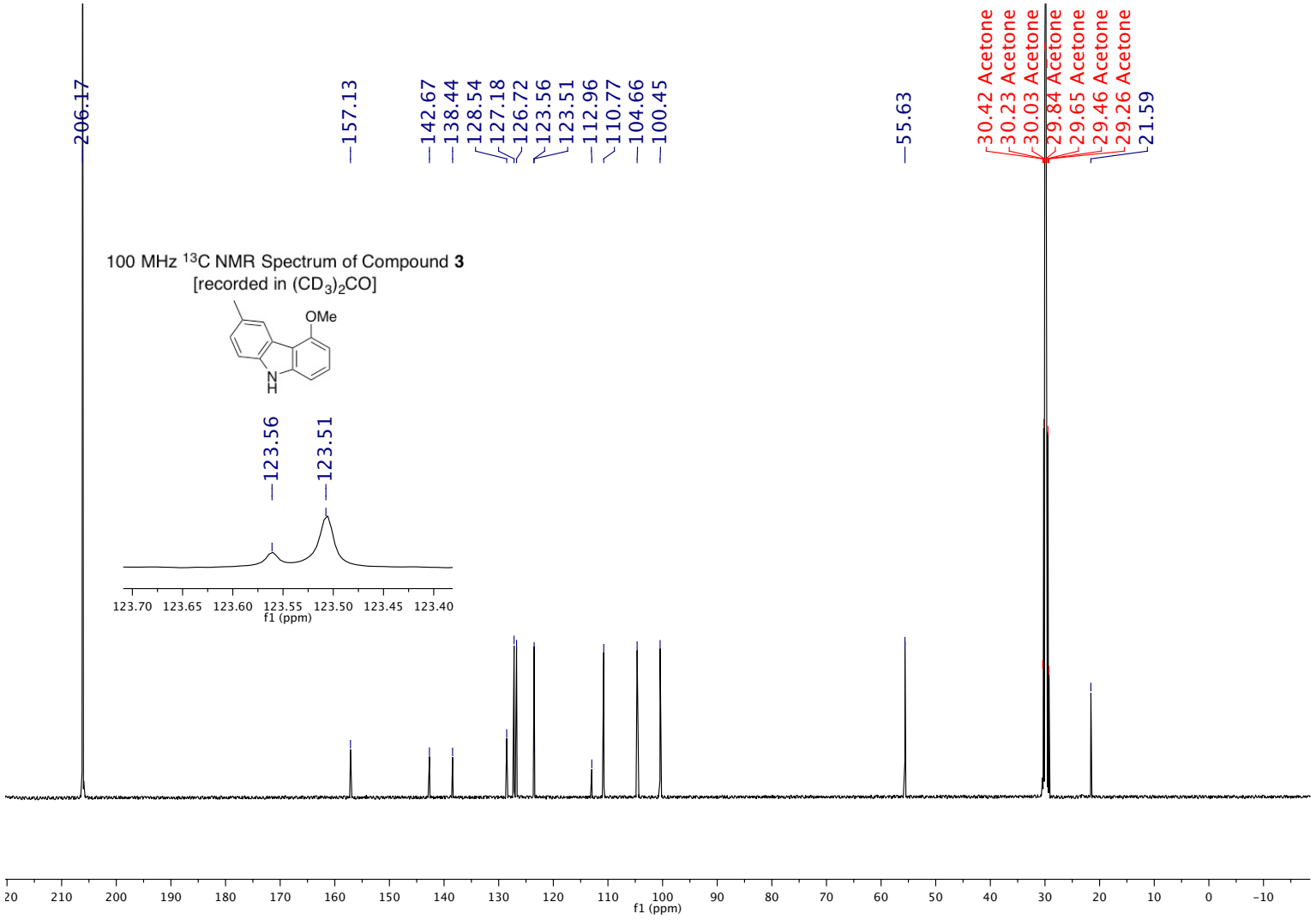
400 MHz ^{1}H NMR Spectrum of Compound **2**
[recorded in $(CD_3)_2CO$]



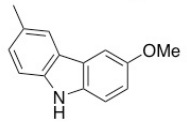

100 MHz ^{13}C NMR Spectrum of Compound **2**
[recorded in $(CD_3)_2CO$]
206.15
141.30
139.24
128.60
127.74
126.21
124.15
123.83
120.77
120.74
119.40
111.64
111.41
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.45 Acetone
29.26 Acetone
21.47
f1 (ppm)

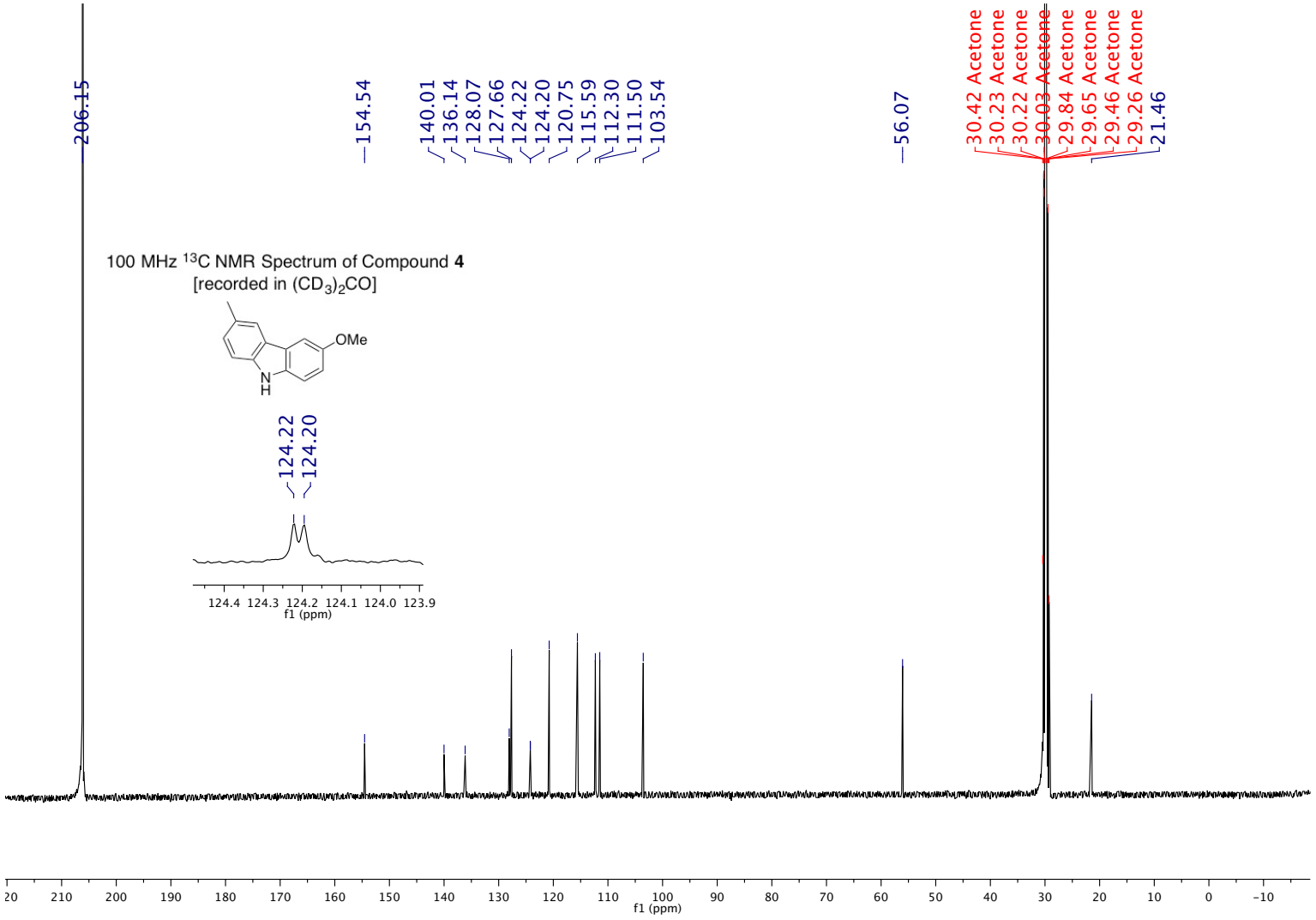
400 MHz ^{1}H NMR Spectrum of Compound **3**
[recorded in $(CD_3)_2CO$]



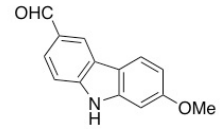

206.17
157.13
142.67
138.44
128.54
127.18
126.72
123.56
123.51
112.96
110.77
104.66
100.45
55.63
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
21.59
100 MHz ^{13}C NMR Spectrum of Compound **3**
[recorded in $(CD_3)_2CO$]
OMe
N
H
123.56
123.51
123.70 123.65 123.60 123.55 123.50 123.45 123.40
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

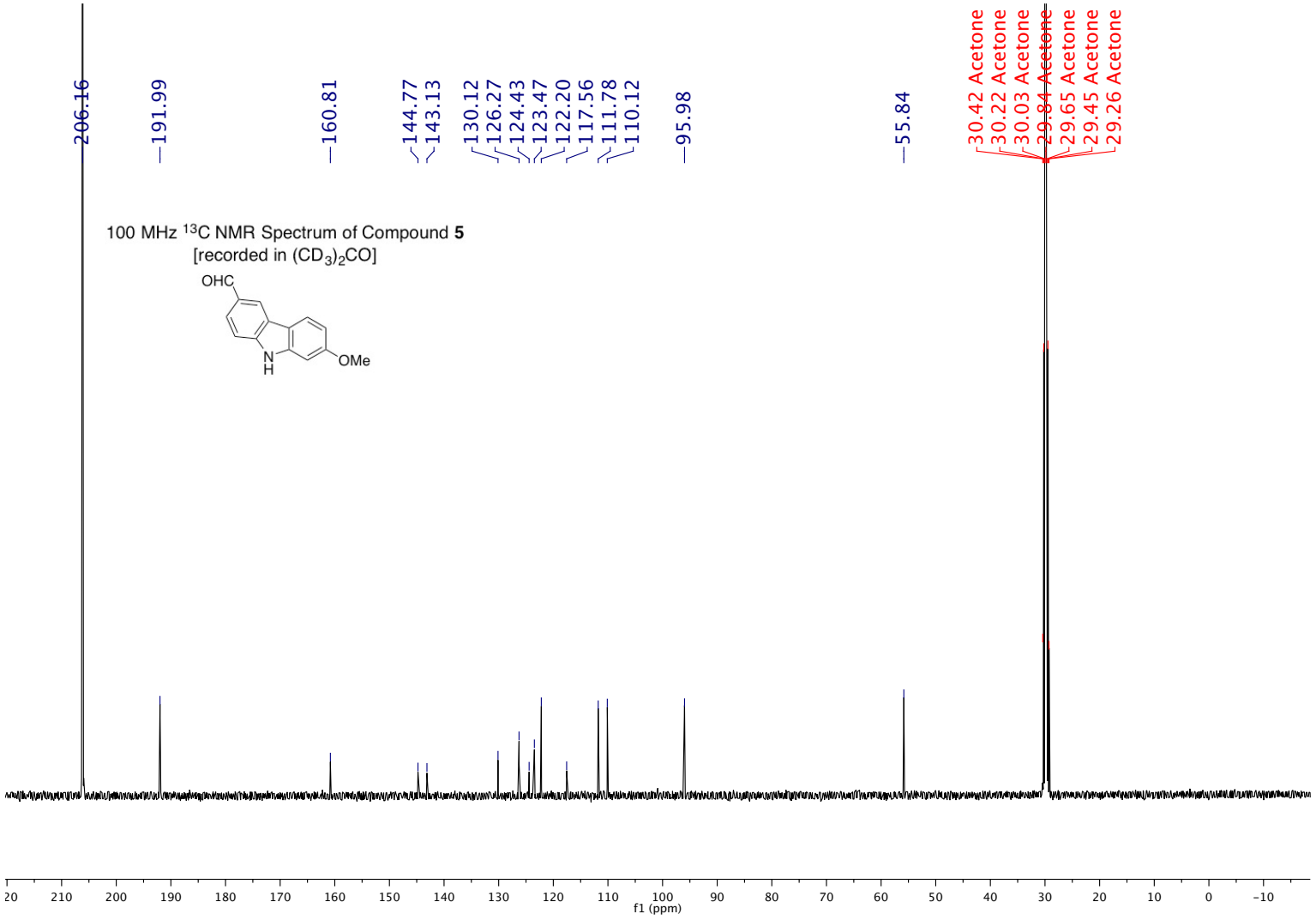
400 MHz ^{1}H NMR Spectrum of Compound **4**
[recorded in $(CD_3)_2CO$]



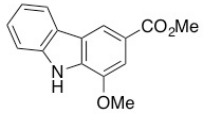

206.15
154.54
140.01
136.14
128.07
127.66
124.22
124.20
120.75
115.59
112.30
111.50
103.54
56.07
30.42 Acetone
30.23 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
21.46
100 MHz ^{13}C NMR Spectrum of Compound **4**
[recorded in $(CD_3)_2CO$]
OMe
N
H
124.22
124.20
124.4 124.3 124.2 124.1 124.0 123.9
f1 (ppm)
f1 (ppm)

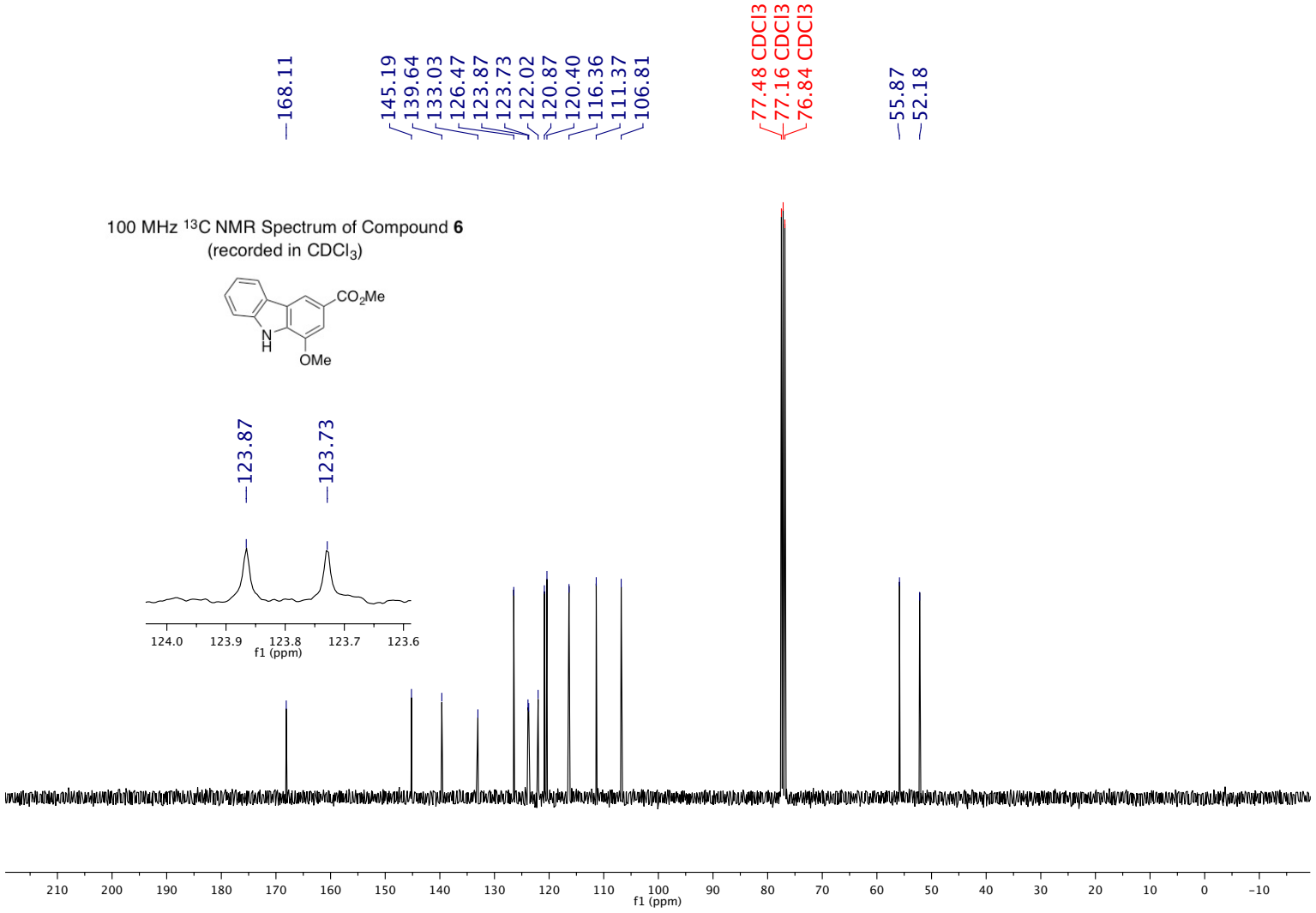
400 MHz ^{1}H NMR Spectrum of Compound **5**
[recorded in $(CD_3)_2CO$]



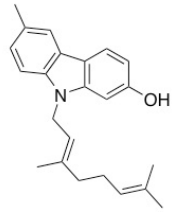

206.16
191.99
160.81
144.77
143.13
130.12
126.27
124.43
123.47
122.20
117.56
111.78
110.12
95.98
55.84
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.45 Acetone
29.26 Acetone
100 MHz ^{13}C NMR Spectrum of Compound **5**
[recorded in $(CD_3)_2CO$]
OHC
N
H
OMe
f1 (ppm)

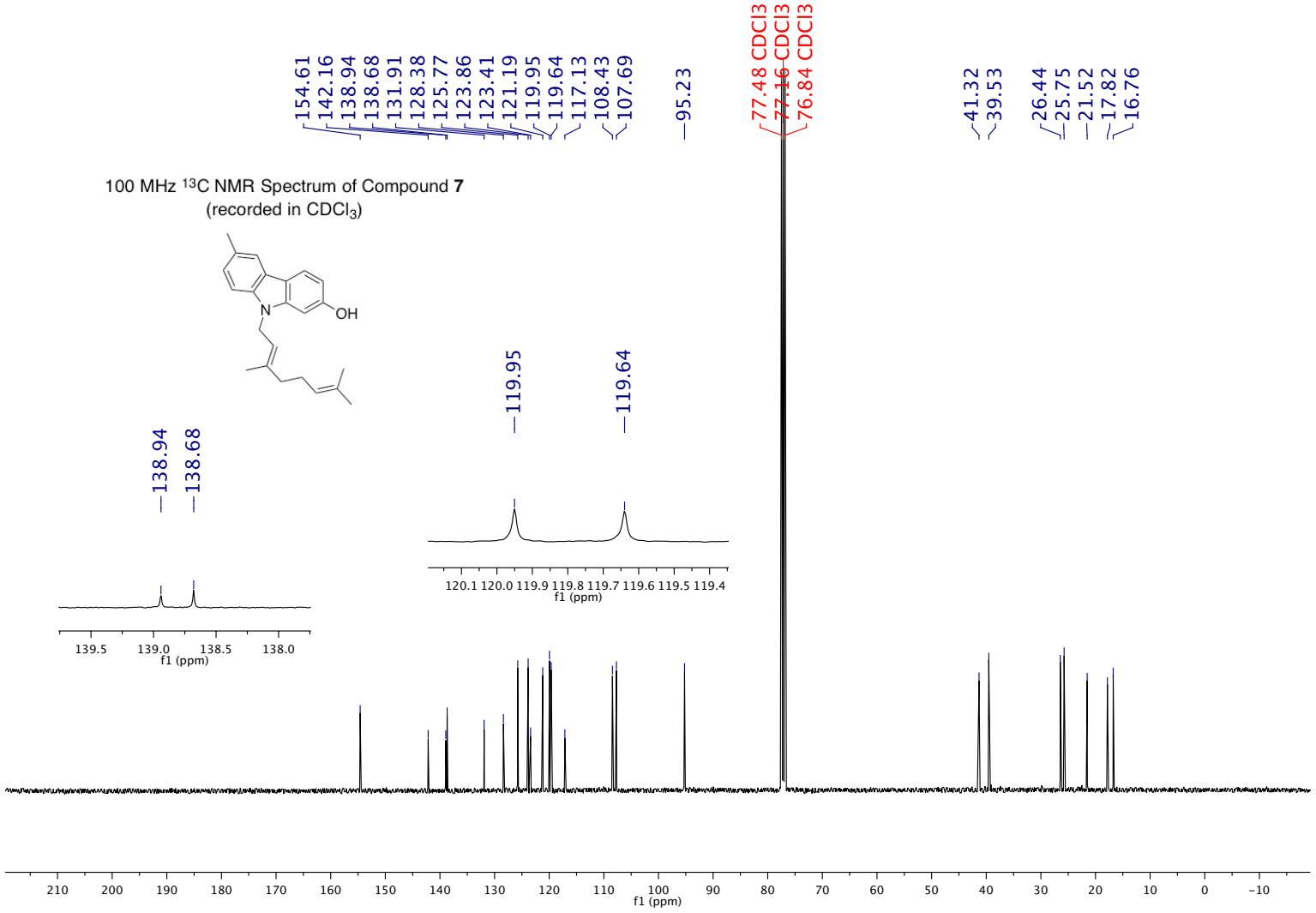
400 MHz ^{1}H NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)



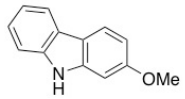

168.11
145.19
139.64
133.03
126.47
123.87
123.73
122.02
120.87
120.40
116.36
111.37
106.81
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.87
52.18
100 MHz 13C NMR Spectrum of Compound 6
(recorded in CDCl3)
CO2Me
N
H
OMe
123.87
123.73
124.0
123.9
123.8
123.7
123.6
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

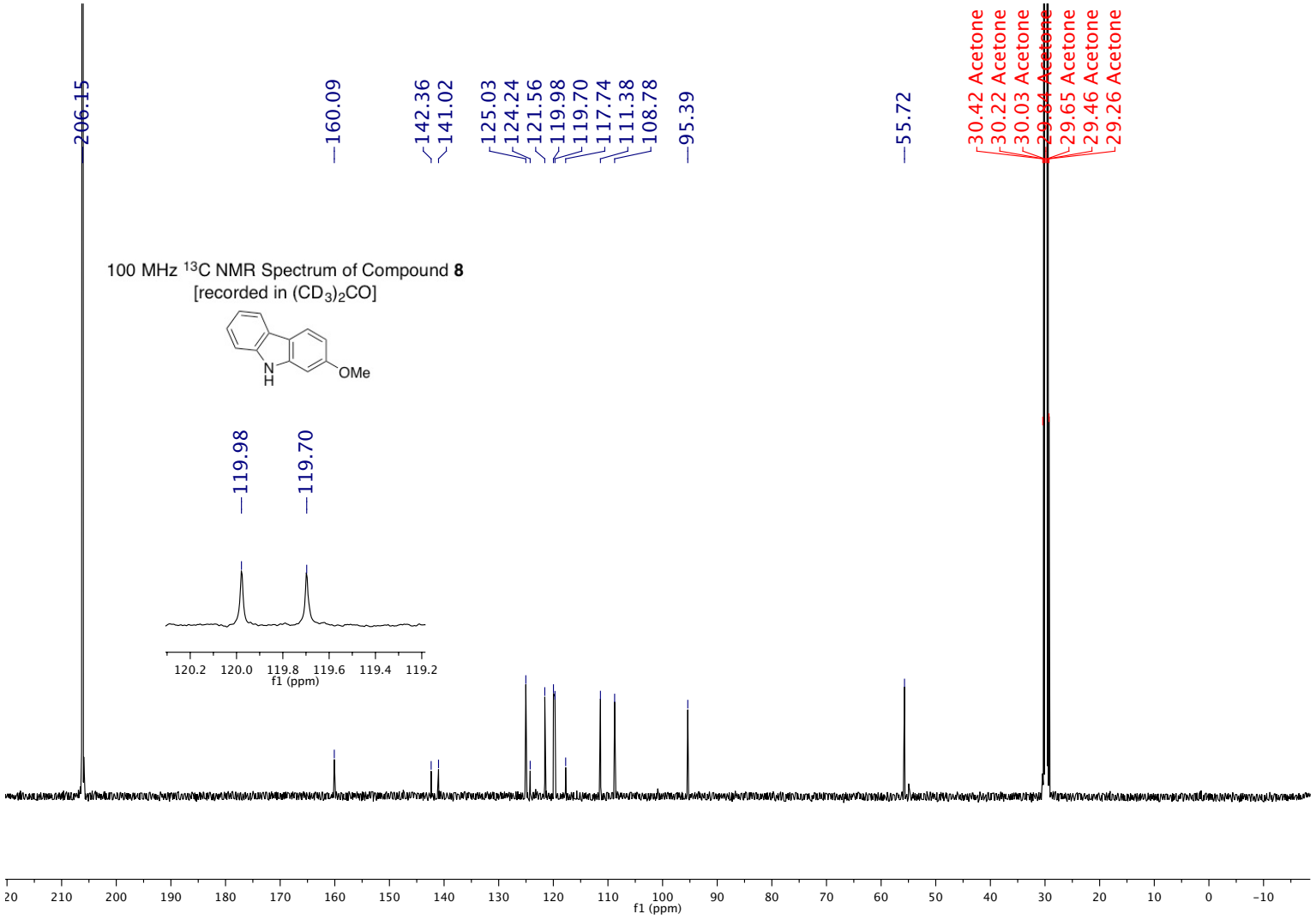
400 MHz ^{1}H NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)



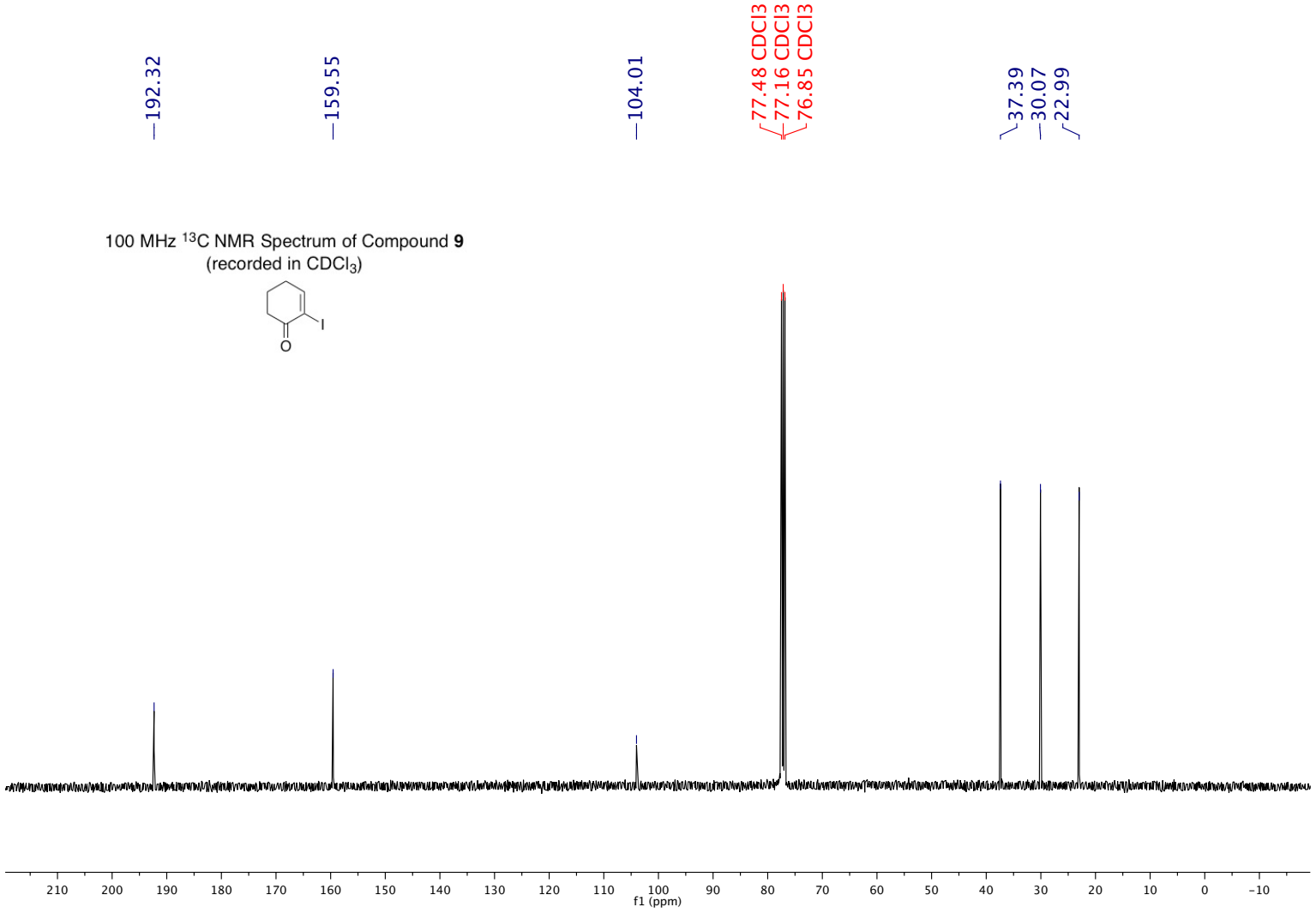

154.61
142.16
138.94
138.68
131.91
128.38
125.77
123.86
123.41
121.19
119.95
119.64
117.13
108.43
107.69
95.23
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
41.32
39.53
26.44
25.75
21.52
17.82
16.76
100 MHz 13C NMR Spectrum of Compound 7
(recorded in CDCl3)
N
OH
138.94
138.68
139.5 139.0 138.5 138.0
f1 (ppm)
119.95
119.64
120.1 120.0 119.9 119.8 119.7 119.6 119.5 119.4
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **8**
[recorded in $(CD_3)_2CO$]

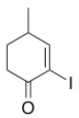


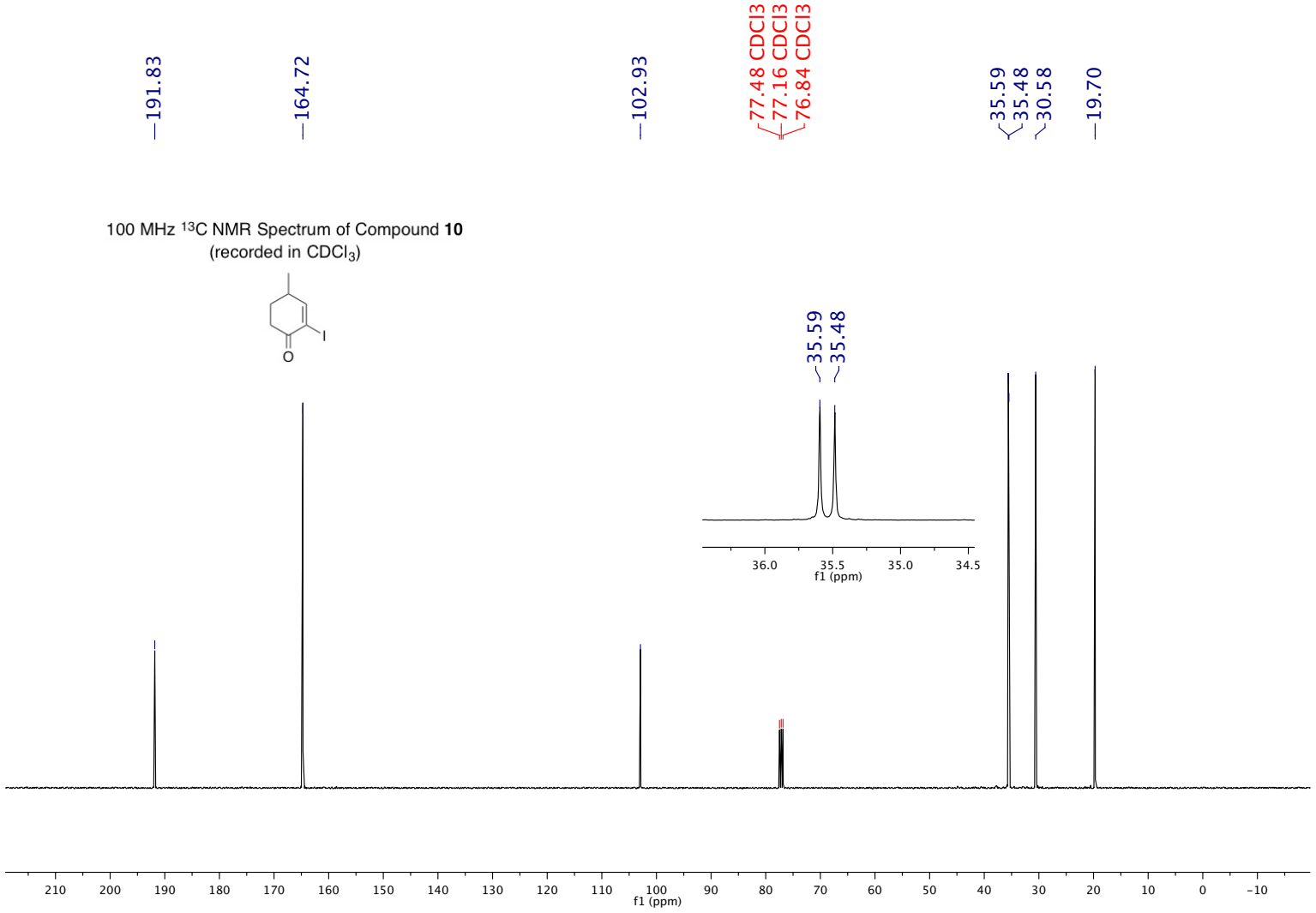

206.15
160.09
142.36
141.02
125.03
124.24
121.56
119.98
119.70
117.74
111.38
108.78
95.39
55.72
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
100 MHz ^{13}C NMR Spectrum of Compound **8**
[recorded in $(CD_3)_2CO$]
N
H
OMe
119.98
119.70
120.2 120.0 119.8 119.6 119.4 119.2
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)

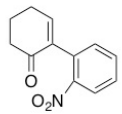

192.32
159.55
104.01
77.48 CDCl3
77.16 CDCl3
76.85 CDCl3
37.39
30.07
22.99
100 MHz 13C NMR Spectrum of Compound 9
(recorded in CDCl3)
I
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

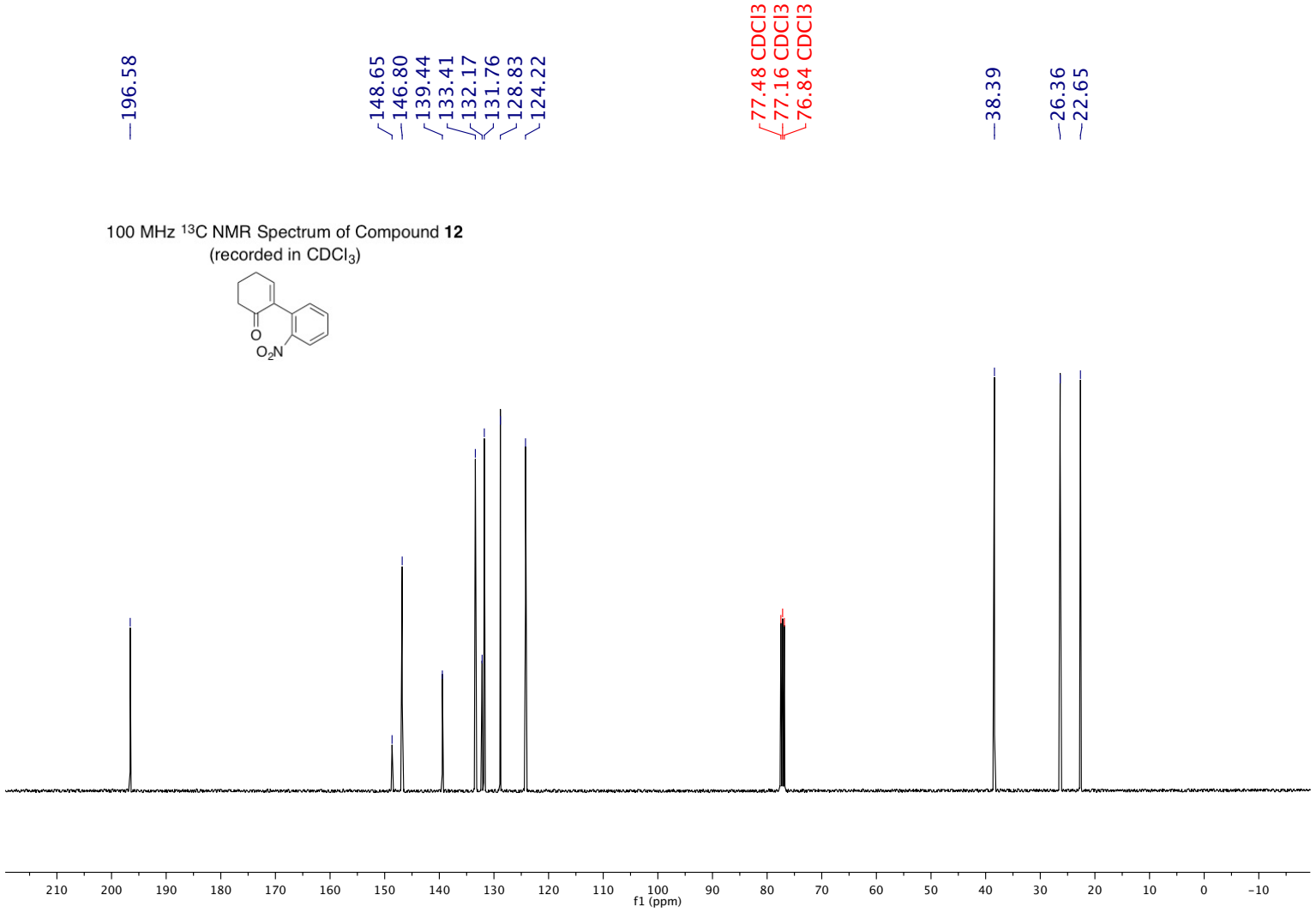
400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



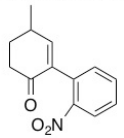

191.83
164.72
102.93
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
35.59
35.48
30.58
19.70
100 MHz 13C NMR Spectrum of Compound 10
(recorded in CDCl3)
I
O
35.59
35.48
36.0
35.5
35.0
34.5
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

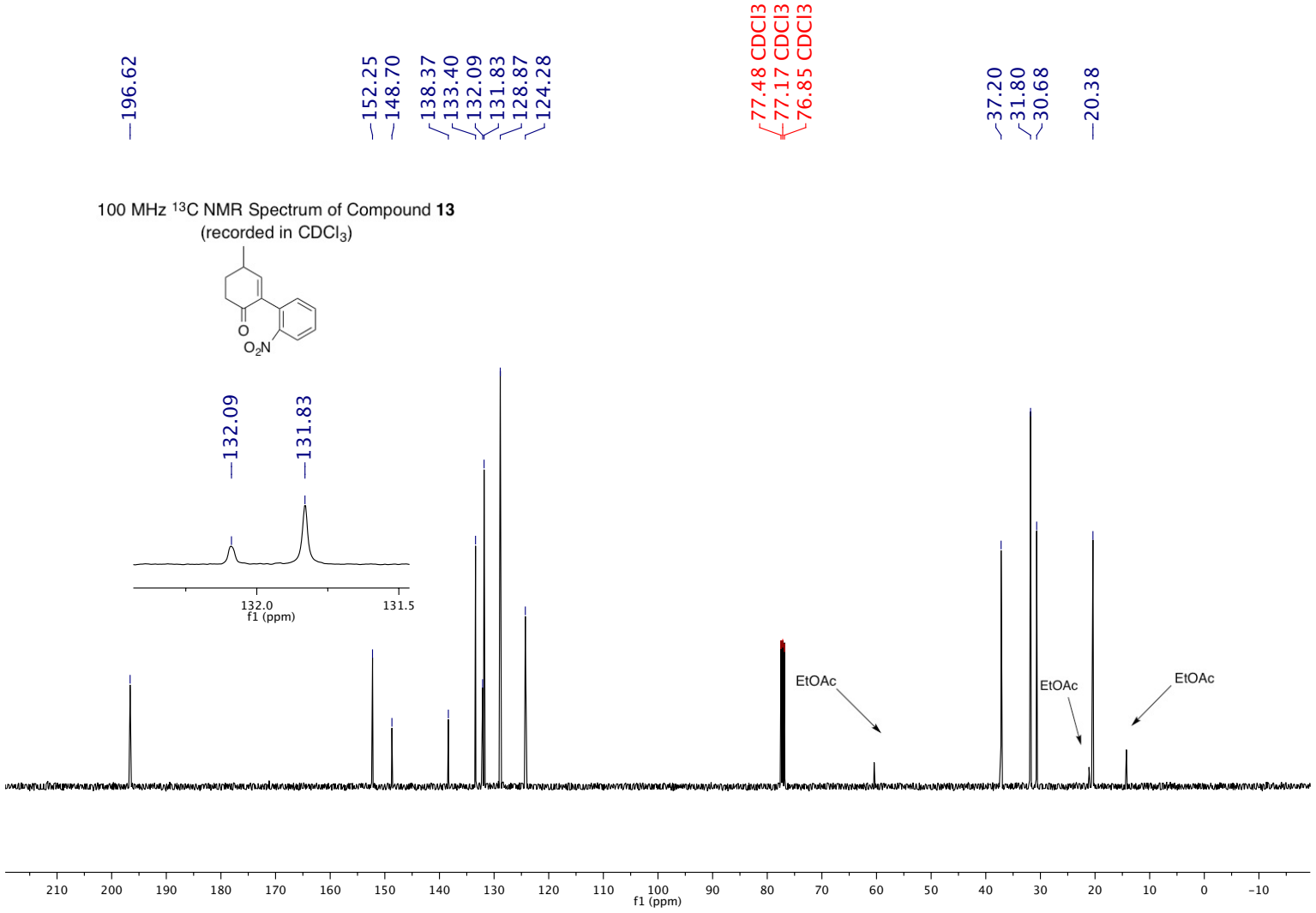
400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)



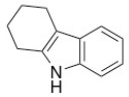

196.58
148.65
146.80
139.44
133.41
132.17
131.76
128.83
124.22
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.39
26.36
22.65
100 MHz 13C NMR Spectrum of Compound 12
(recorded in CDCl3)
O
O2N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

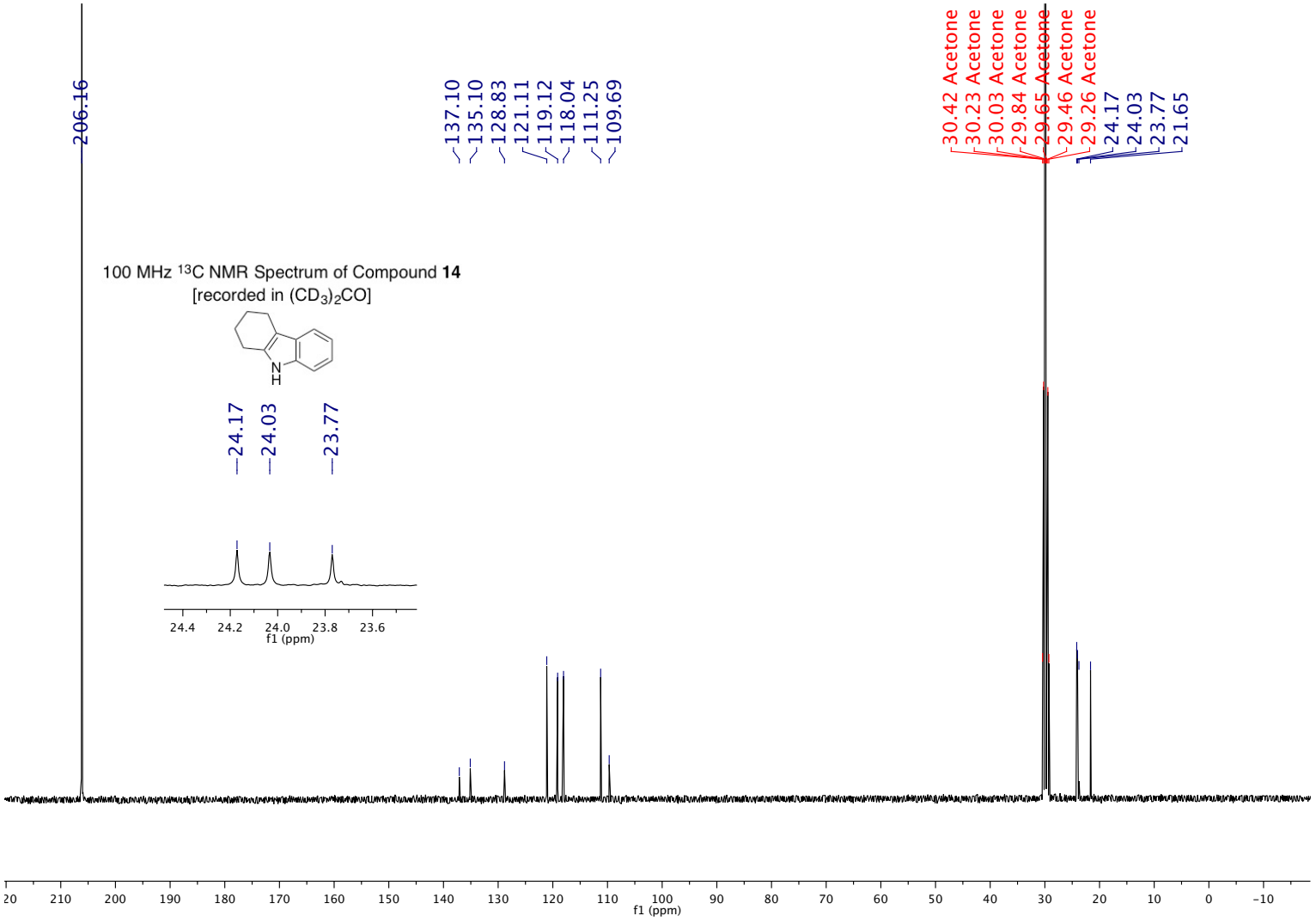
400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)



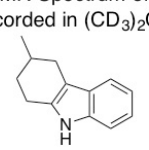

196.62
152.25
148.70
138.37
133.40
132.09
131.83
128.87
124.28
77.48 CDCl3
77.17 CDCl3
76.85 CDCl3
37.20
31.80
30.68
20.38
100 MHz 13C NMR Spectrum of Compound 13
(recorded in CDCl3)
O
O2N
132.09
131.83
132.0
131.5
f1 (ppm)
EtOAc
EtOAc
EtOAc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

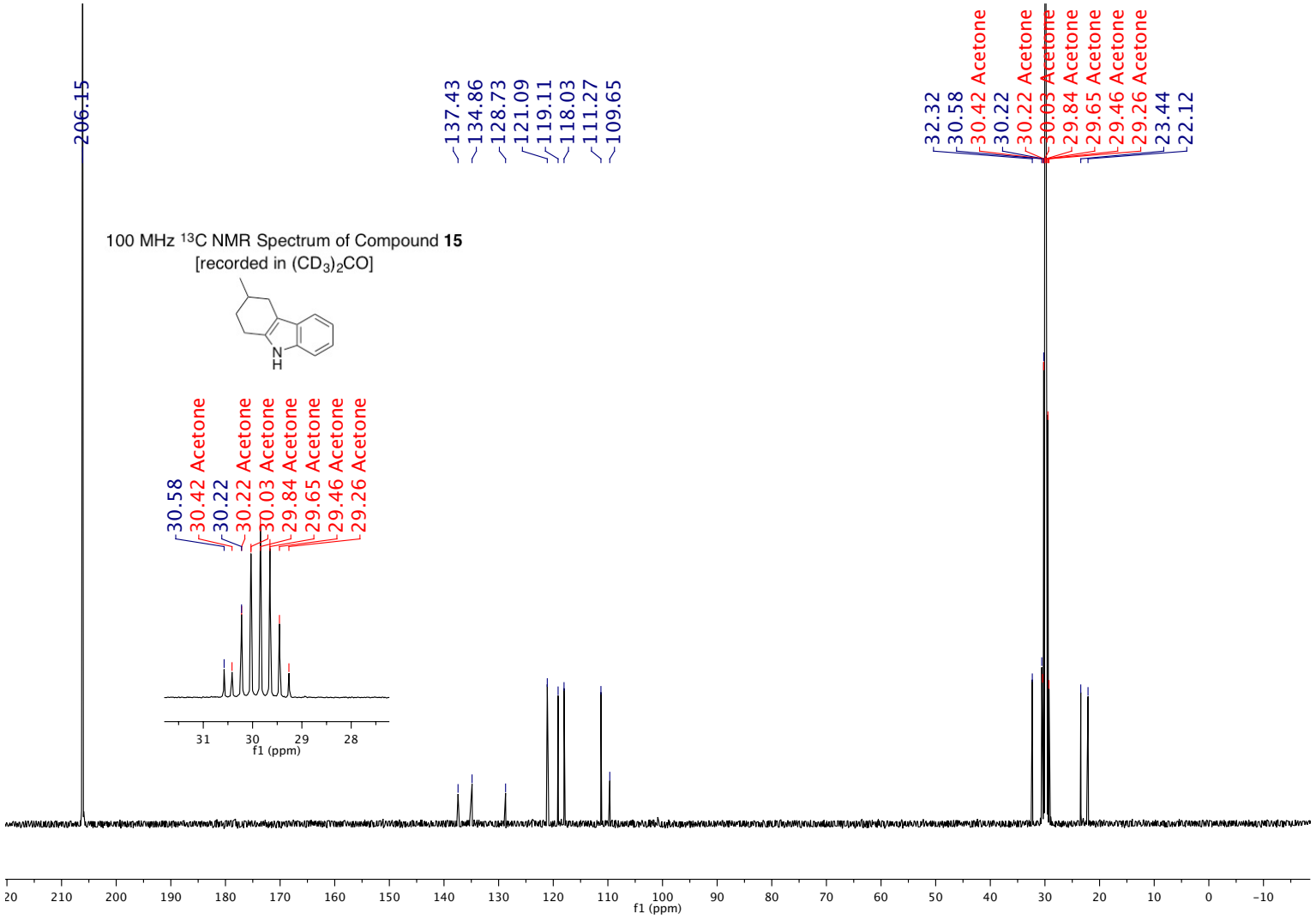
400 MHz ^{1}H NMR Spectrum of Compound **14**
[recorded in $(CD_3)_2CO$]



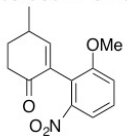

206.16
137.10
135.10
128.83
121.11
119.12
118.04
111.25
109.69
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
24.17
24.03
23.77
21.65
100 MHz ^{13}C NMR Spectrum of Compound **14**
[recorded in $(CD_3)_2CO$]
N
H
24.17
24.03
23.77
24.4 24.2 24.0 23.8 23.6
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

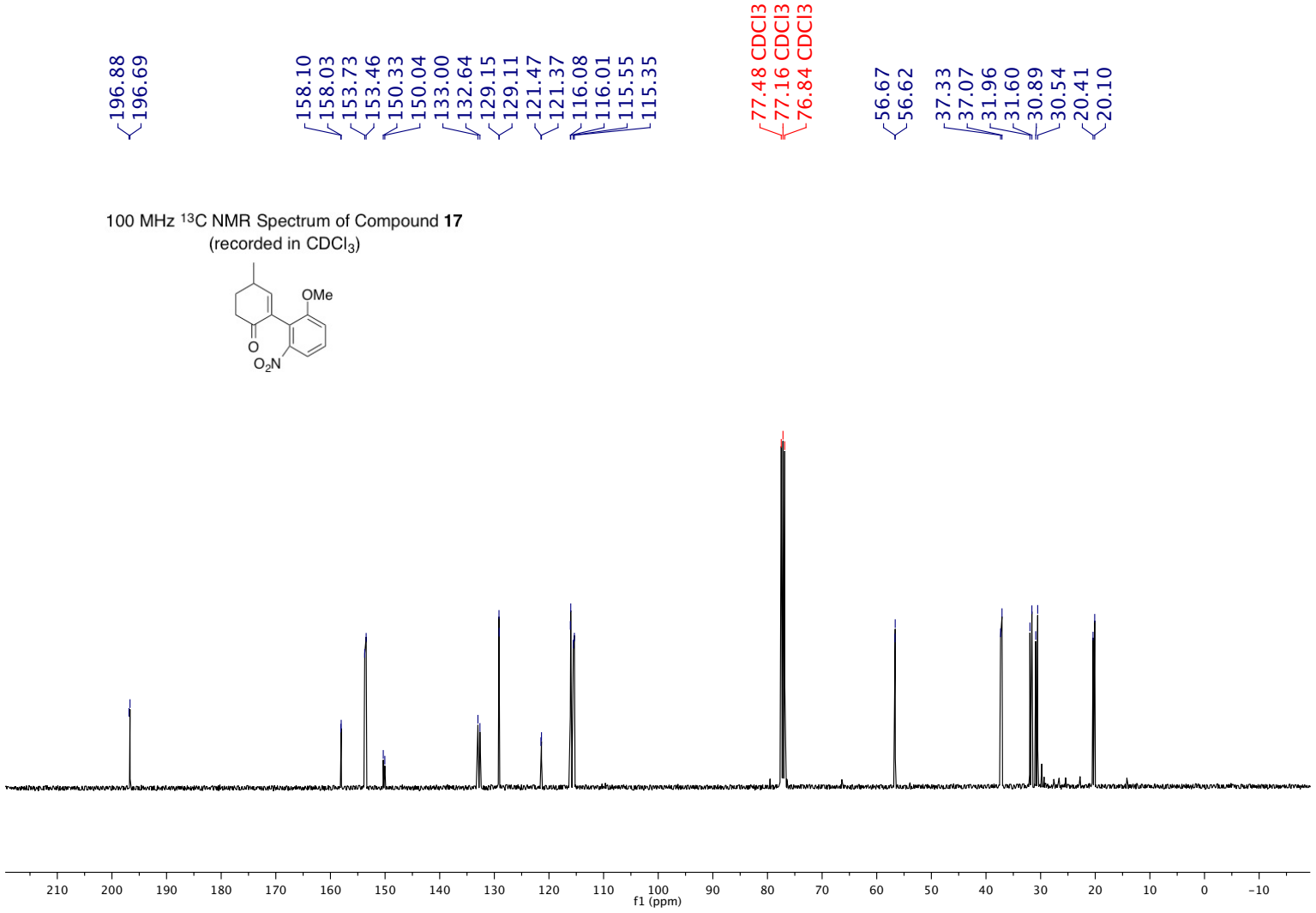
400 MHz ^{1}H NMR Spectrum of Compound **15**
[recorded in $(CD_3)_2CO$]




100 MHz ^{13}C NMR Spectrum of Compound **15**
[recorded in $(CD_3)_2CO$]
206.15
137.43
134.86
128.73
121.09
119.11
118.03
111.27
109.65
32.32
30.58
30.42 Acetone
30.22
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
23.44
22.12
f1 (ppm)

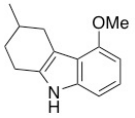
400 MHz ^{1}H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

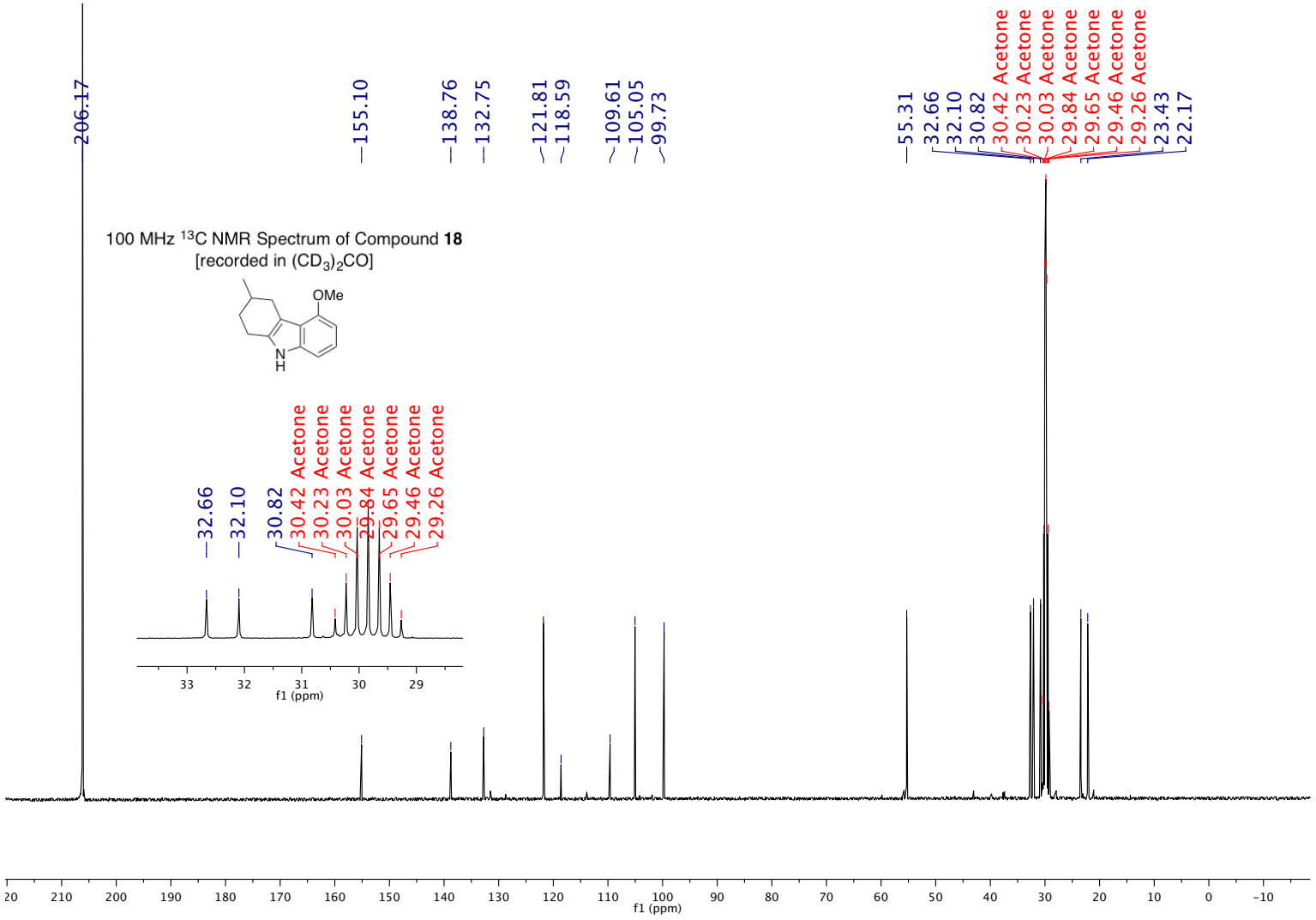




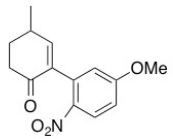
100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

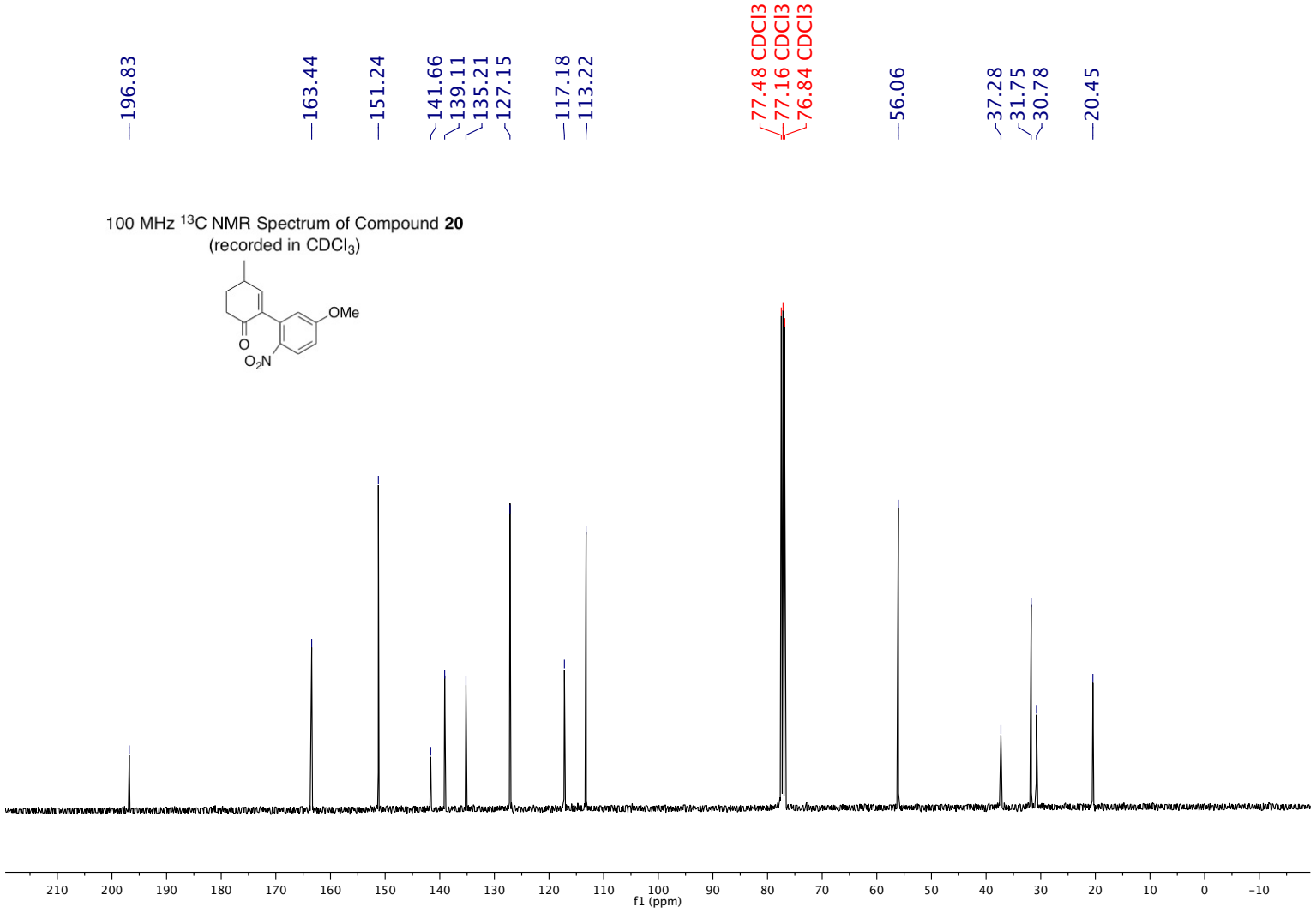
400 MHz ^{1}H NMR Spectrum of Compound **18**
[recorded in $(CD_3)_2CO$]



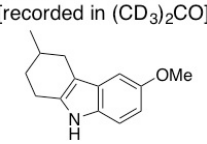

100 MHz ^{13}C NMR Spectrum of Compound **18**
[recorded in $(CD_3)_2CO$]
OMe
N
H
206.17
155.10
138.76
132.75
121.81
118.59
109.61
105.05
99.73
55.31
32.66
32.10
30.82
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
23.43
22.17
f1 (ppm)

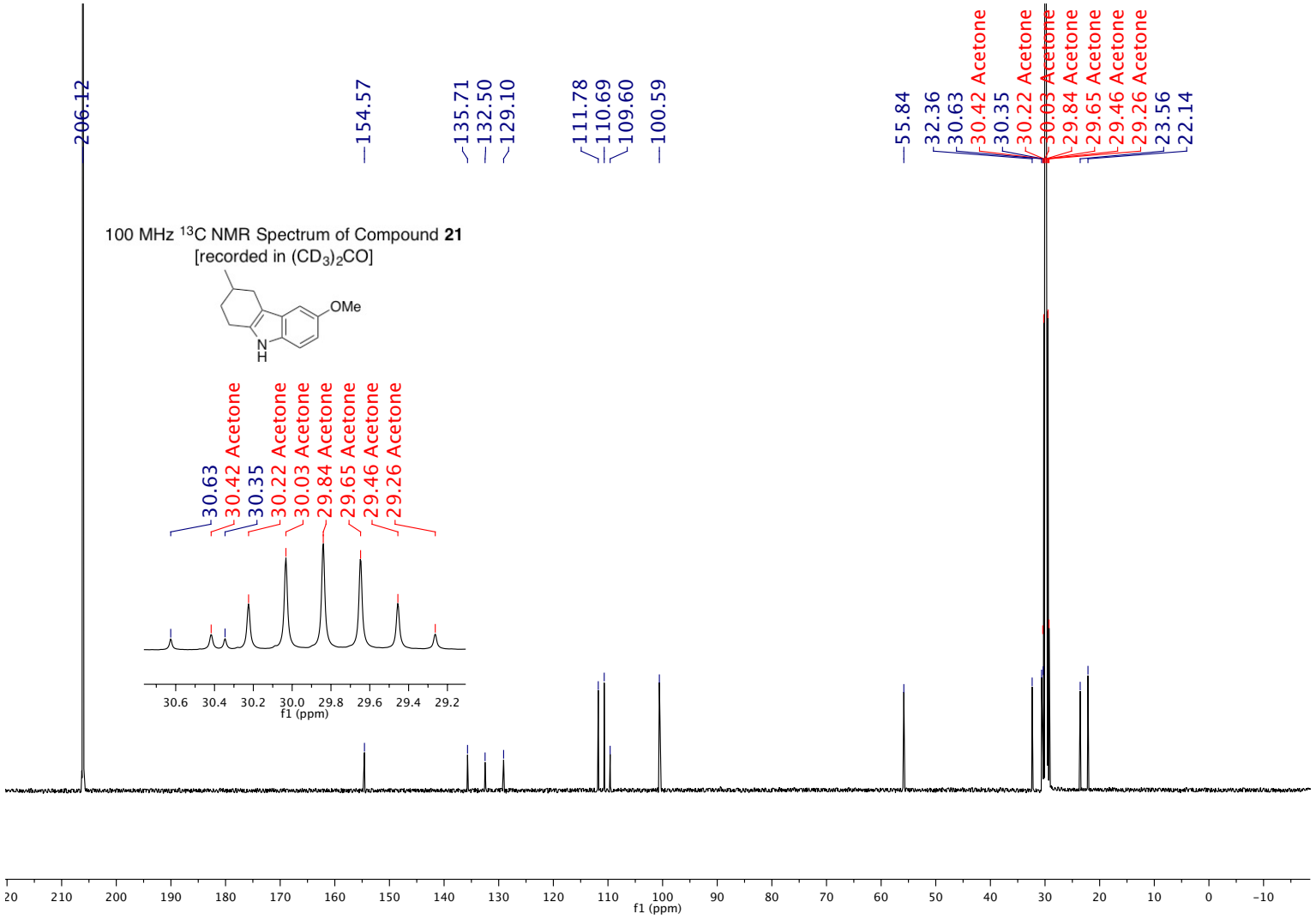
400 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in $CDCl_3$)



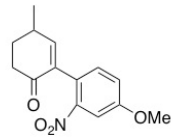

196.83
163.44
151.24
141.66
139.11
135.21
127.15
117.18
113.22
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.06
37.28
31.75
30.78
20.45
100 MHz 13C NMR Spectrum of Compound 20
(recorded in CDCl3)
OMe
O
O2N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

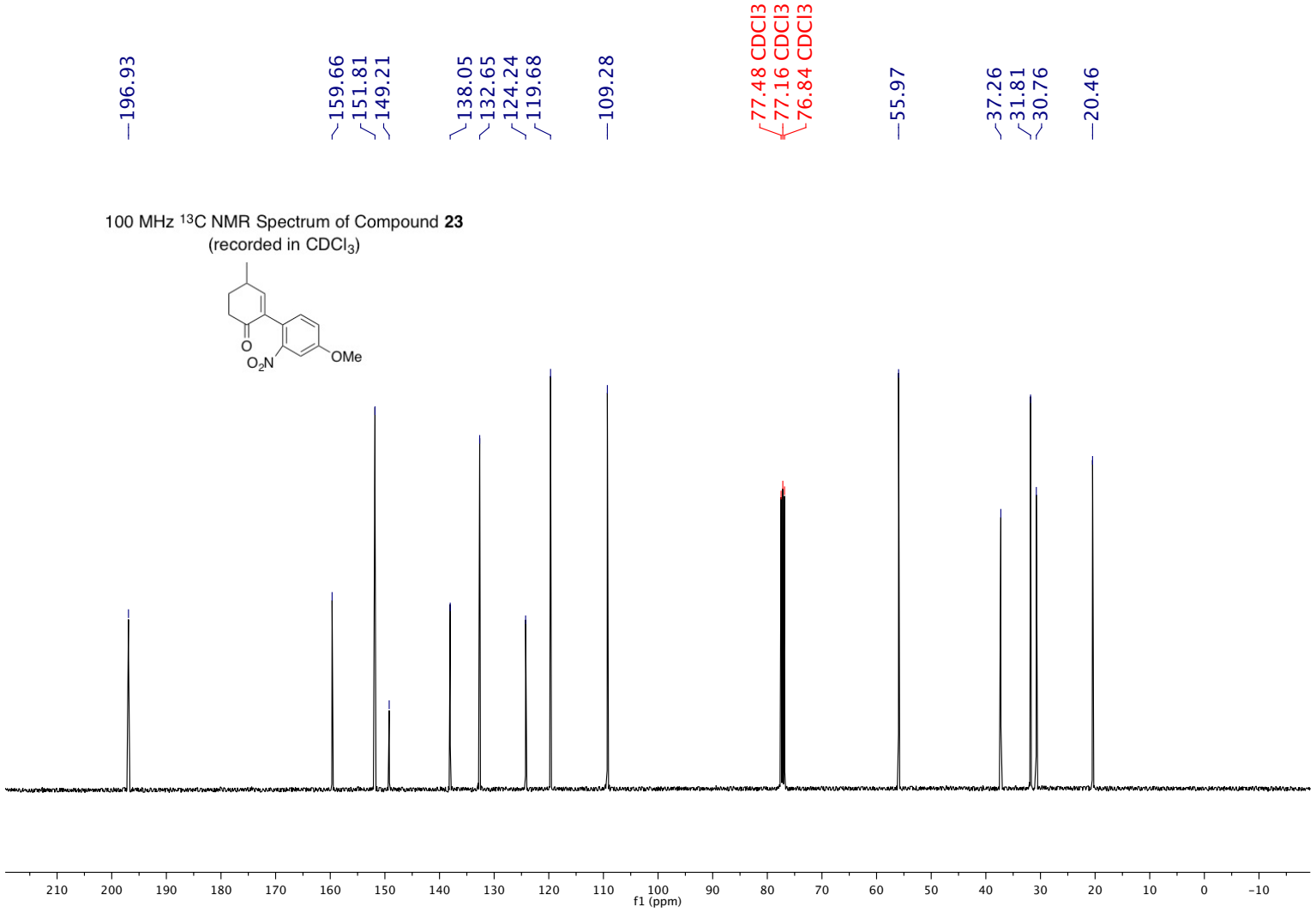
400 MHz ^{1}H NMR Spectrum of Compound **21**
[recorded in $(CD_3)_2CO$]



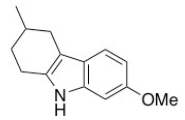

100 MHz ^{13}C NMR Spectrum of Compound **21**
[recorded in $(CD_3)_2CO$]
OMe
N
H
206.12
154.57
135.71
132.50
129.10
111.78
110.69
109.60
100.59
55.84
32.36
30.63
30.42 Acetone
30.35
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
23.56
22.14
f1 (ppm)

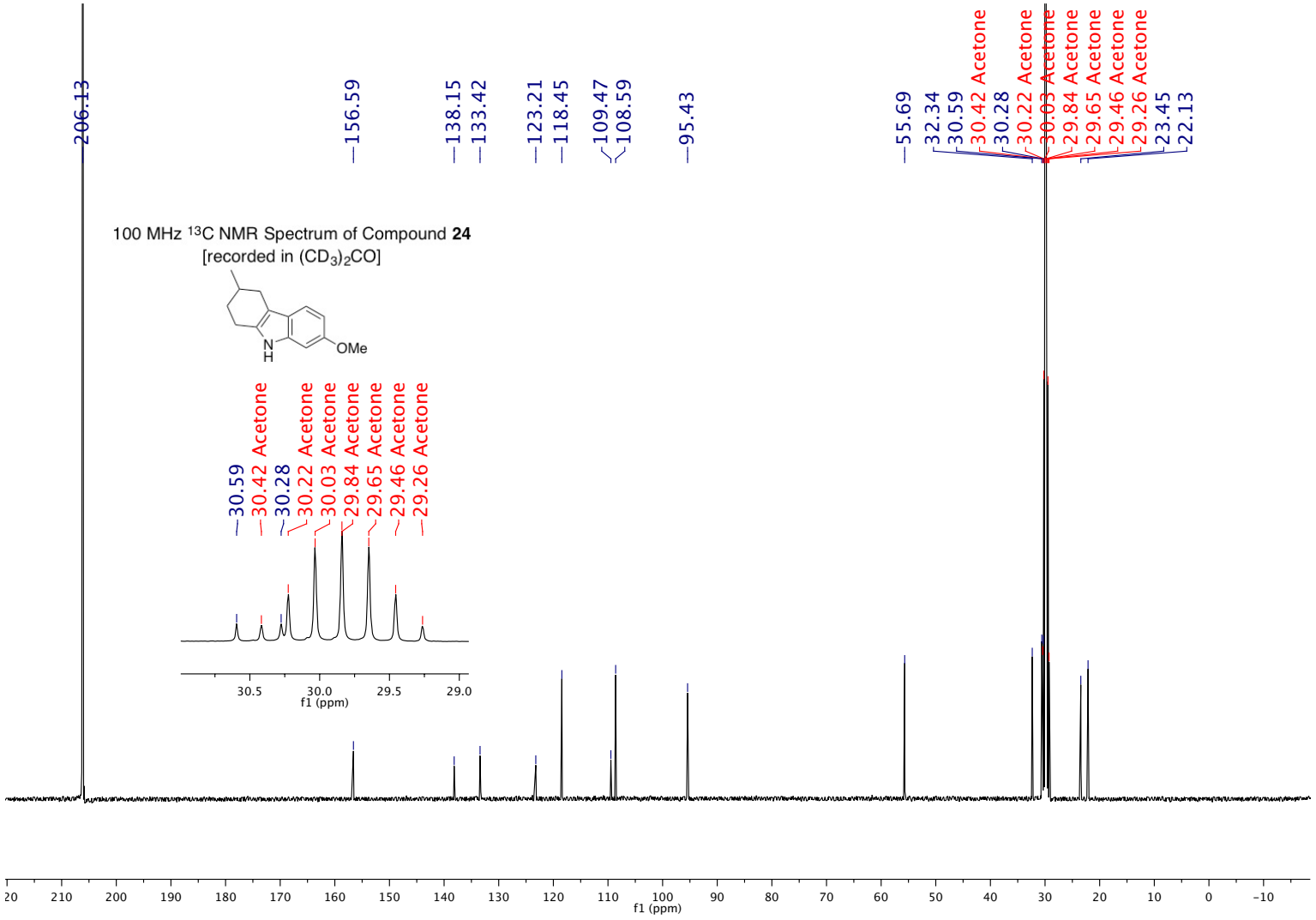
400 MHz ^{1}H NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)

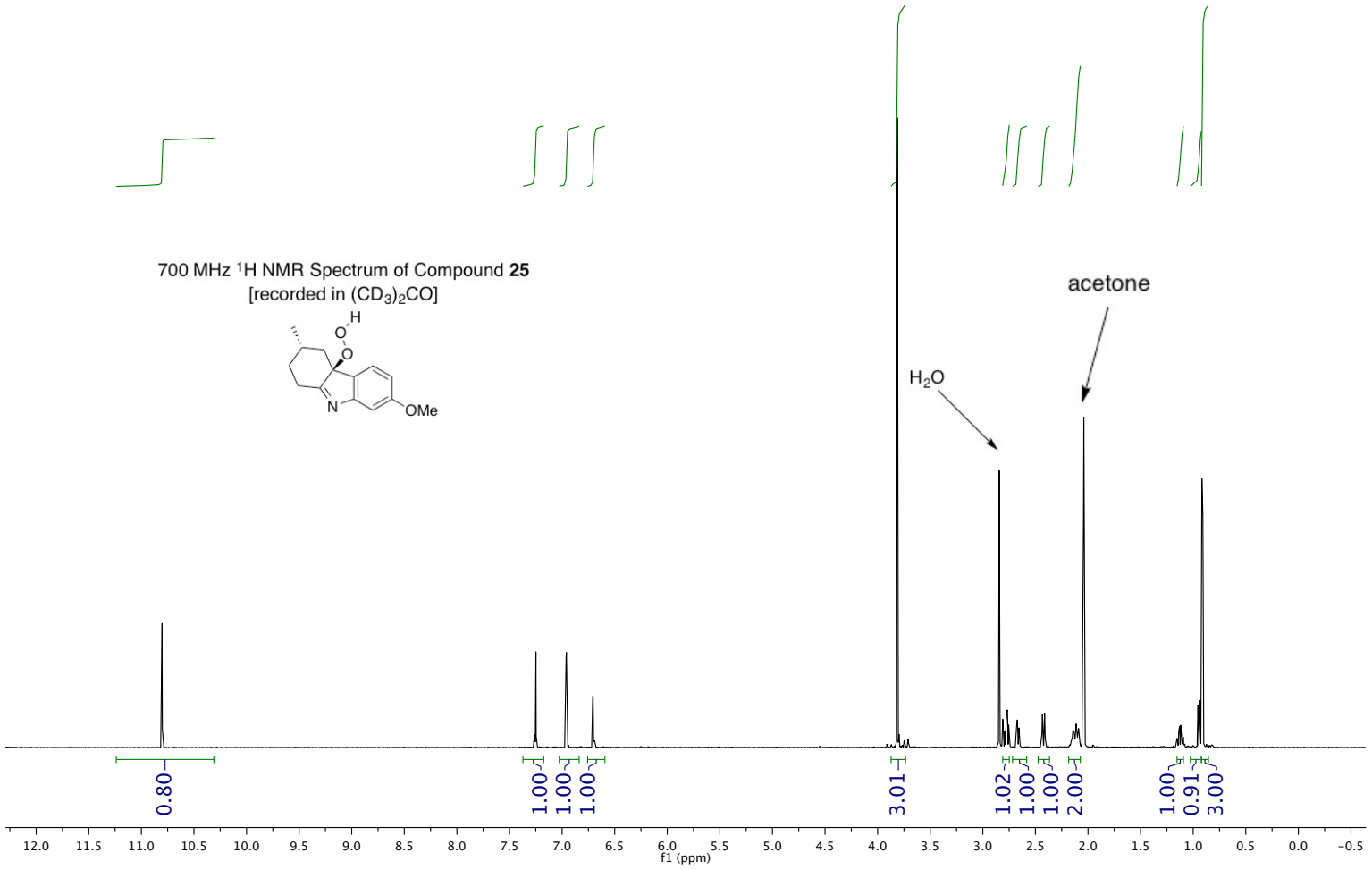


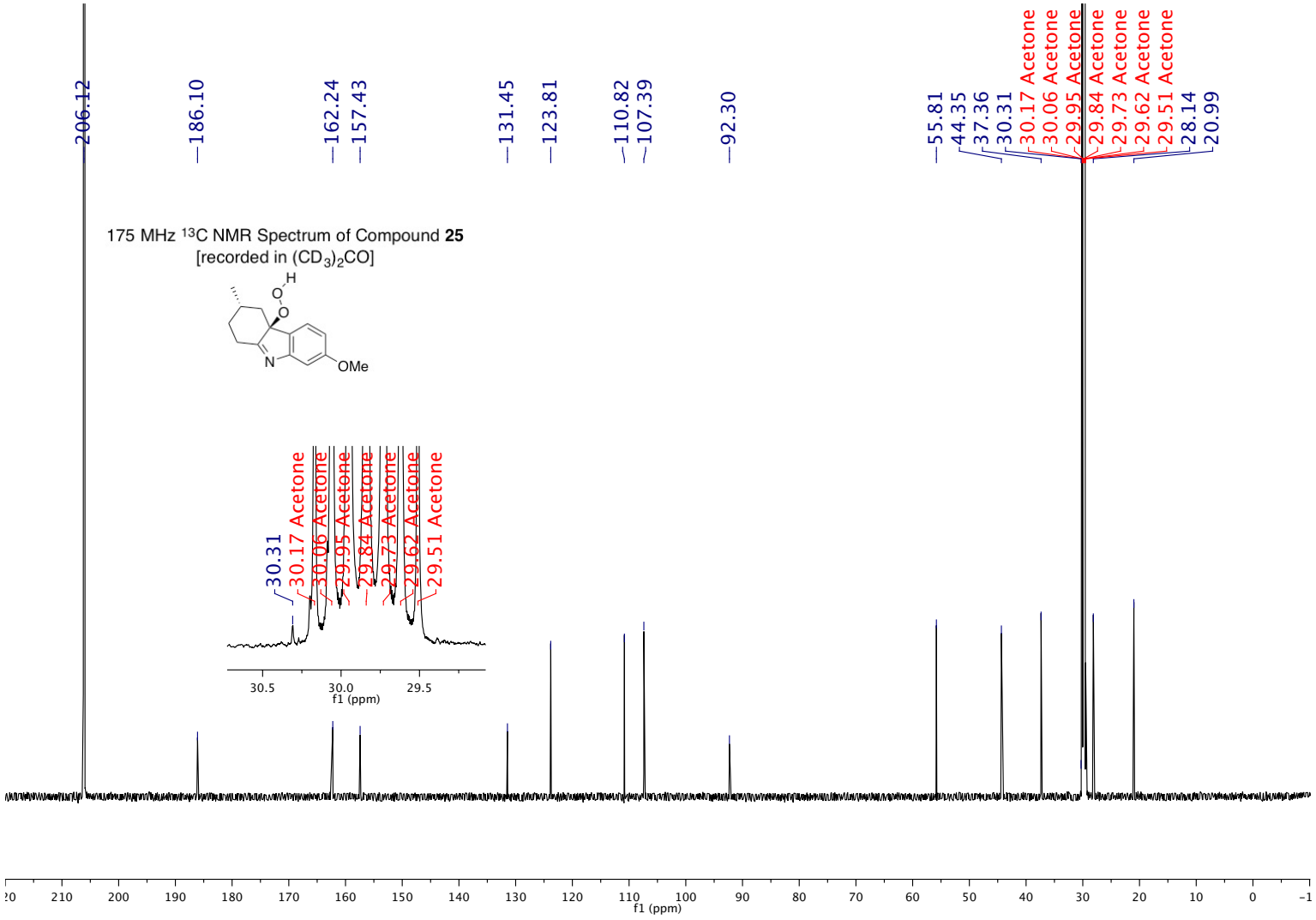

196.93
159.66
151.81
149.21
138.05
132.65
124.24
119.68
109.28
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.97
37.26
31.81
30.76
20.46
100 MHz 13C NMR Spectrum of Compound 23
(recorded in CDCl3)
O
O2N
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **24**
[recorded in $(CD_3)_2CO$]

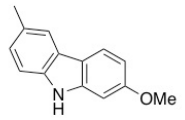


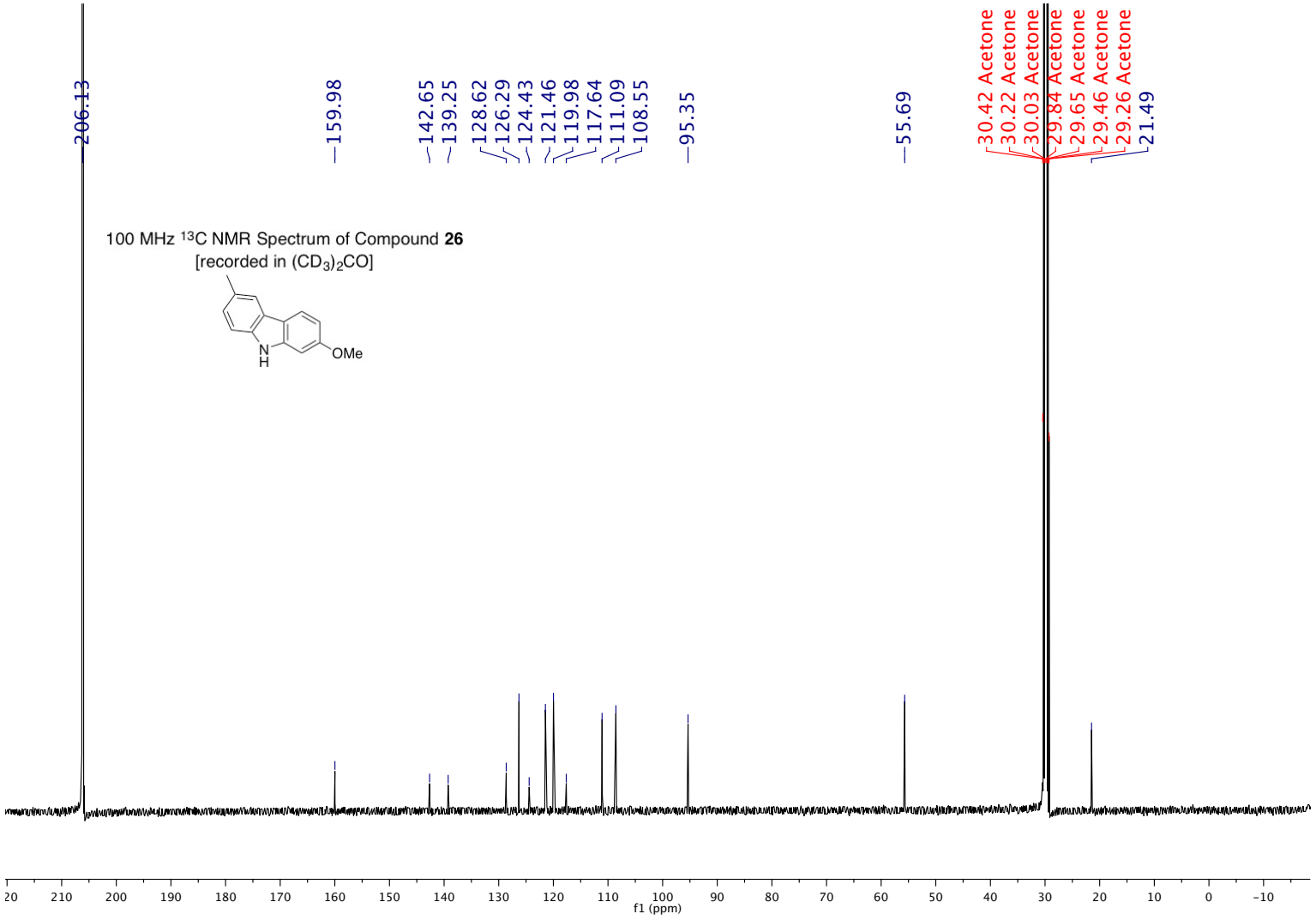

206.13
156.59
138.15
133.42
123.21
118.45
109.47
108.59
95.43
55.69
32.34
30.59
30.42 Acetone
30.28
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
23.45
22.13
100 MHz ^{13}C NMR Spectrum of Compound **24**
[recorded in $(CD_3)_2CO$]
N
H
OMe
30.59
30.42 Acetone
30.28
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
30.5
30.0
29.5
29.0
f1 (ppm)
f1 (ppm)


700 MHz ¹H NMR Spectrum of Compound 25
[recorded in (CD3)2CO]
H
O
O
N
OMe
H2O
acetone
0.80
1.00
1.00
1.00
3.01
1.02
1.00
1.00
2.00
1.00
0.91
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

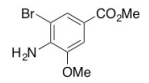

206.12
186.10
162.24
157.43
131.45
123.81
110.82
107.39
92.30
55.81
44.35
37.36
30.31
30.17 Acetone
30.06 Acetone
29.95 Acetone
29.84 Acetone
29.73 Acetone
29.62 Acetone
29.51 Acetone
28.14
20.99
175 MHz 13C NMR Spectrum of Compound 25
[recorded in (CD3)2CO]
O
H
O
N
OMe
30.31
30.17 Acetone
30.06 Acetone
29.95 Acetone
29.84 Acetone
29.73 Acetone
29.62 Acetone
29.51 Acetone
30.5
30.0
29.5
f1 (ppm)
f1 (ppm)

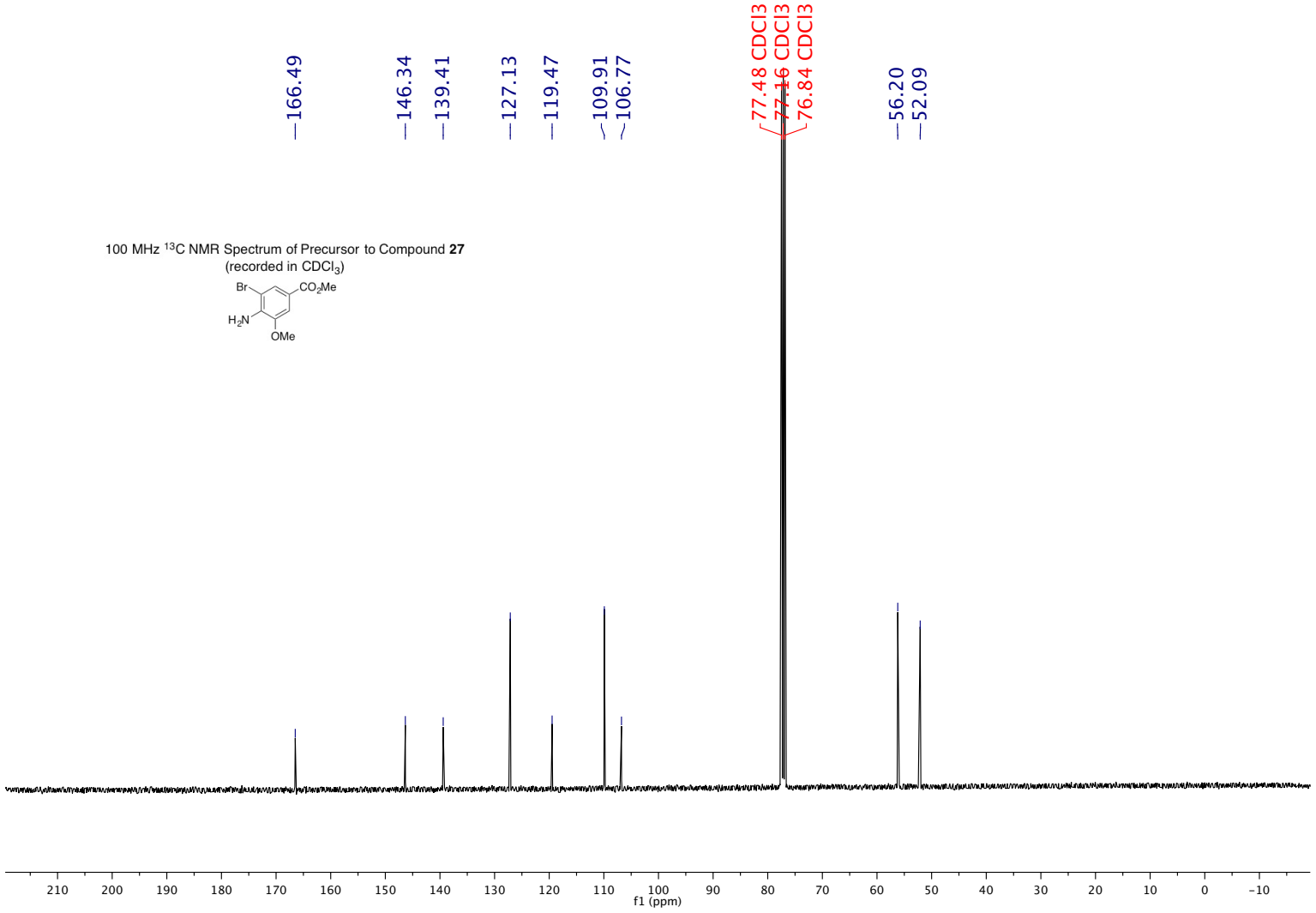
400 MHz ^{1}H NMR Spectrum of Compound **26**
[recorded in $(CD_3)_2CO$]



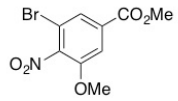

206.13
159.98
142.65
139.25
128.62
126.29
124.43
121.46
119.98
117.64
111.09
108.55
95.35
55.69
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
21.49
100 MHz ^{13}C NMR Spectrum of Compound **26**
[recorded in $(CD_3)_2CO$]
N
H
OMe
f1 (ppm)

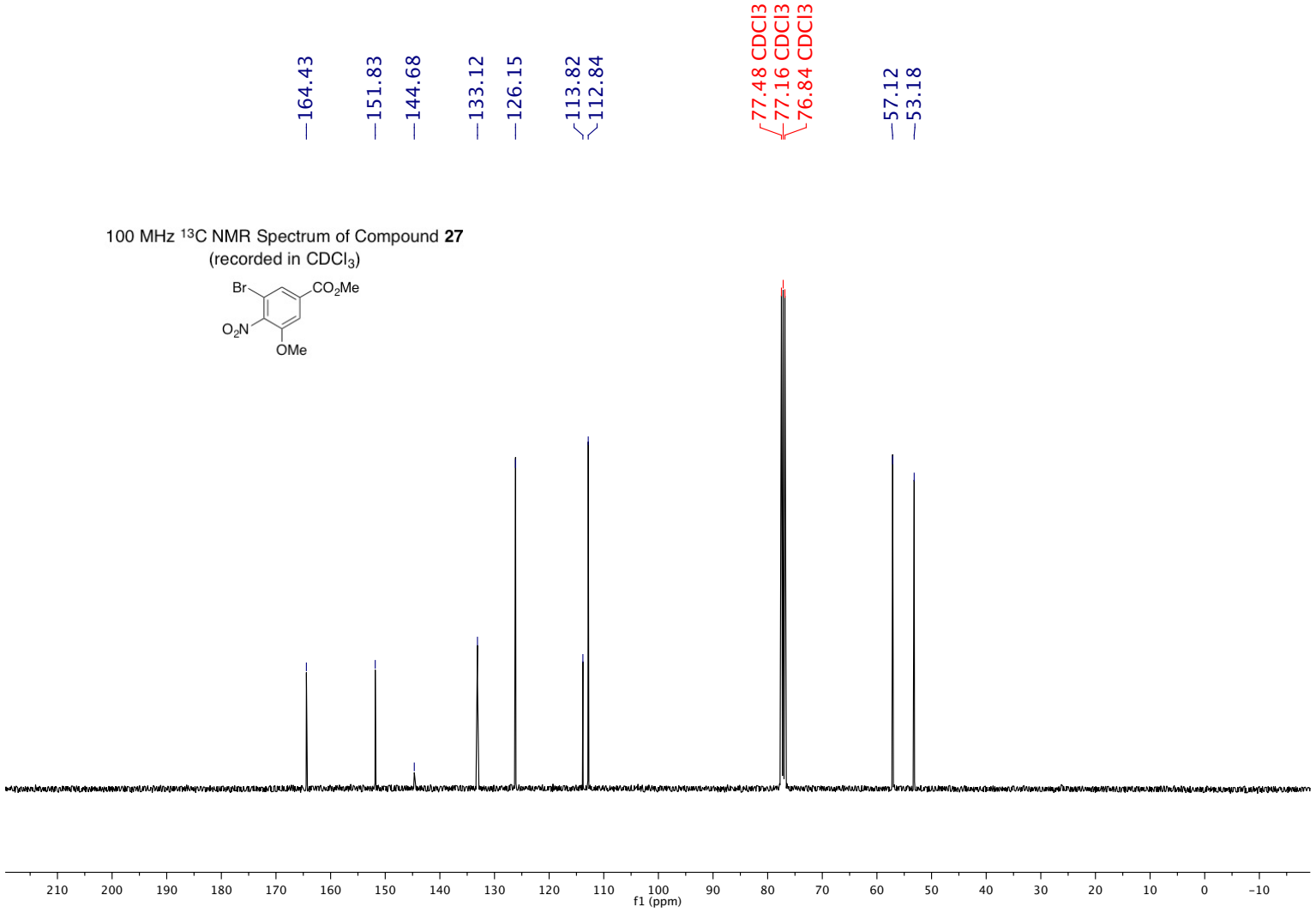
400 MHz ^{1}H NMR Spectrum of Precursor to Compound **27**
(recorded in $CDCl_3$)



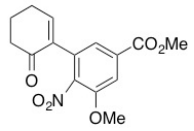

166.49
146.34
139.41
127.13
119.47
109.91
106.77
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.20
52.09
100 MHz ^{13}C NMR Spectrum of Precursor to Compound **27**
(recorded in $CDCl_3$)
Br
CO_2Me
H_2N
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

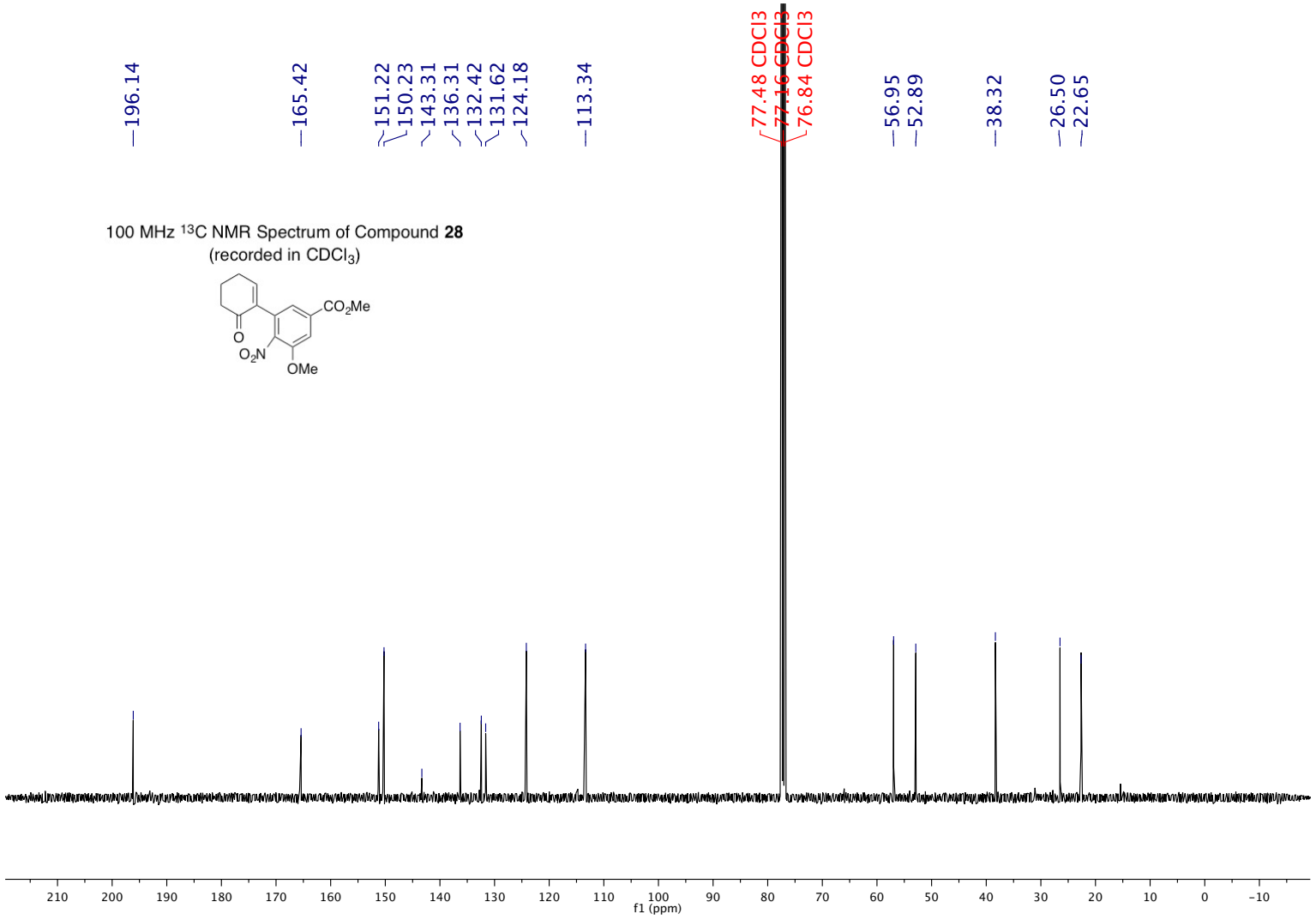
400 MHz ^{1}H NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)



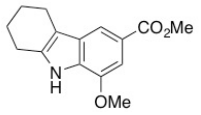

164.43
151.83
144.68
133.12
126.15
113.82
112.84
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
57.12
53.18
100 MHz 13C NMR Spectrum of Compound 27
(recorded in CDCl3)
Br
CO2Me
O2N
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

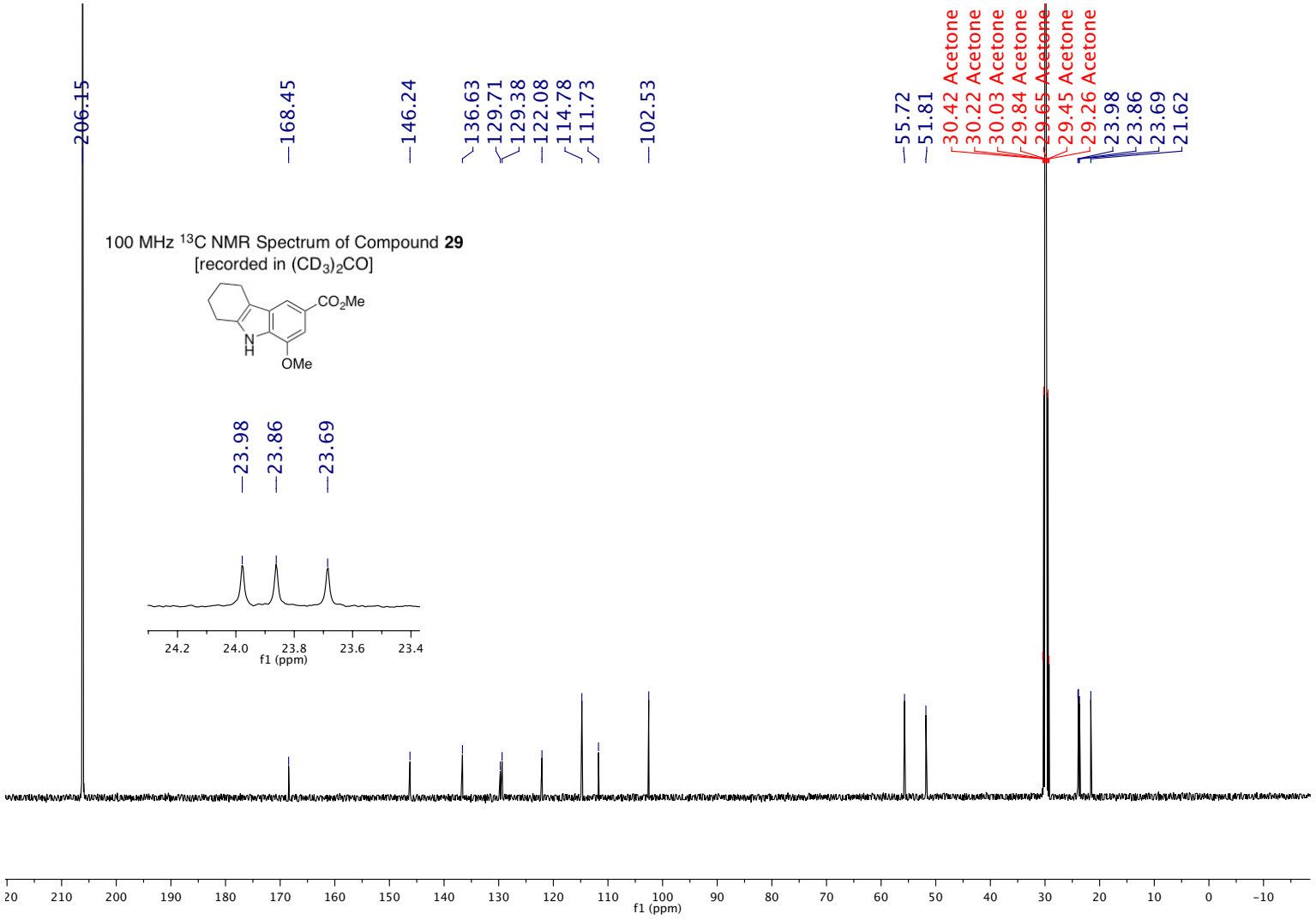
400 MHz ^{1}H NMR Spectrum of Compound **28**
(recorded in $CDCl_3$)



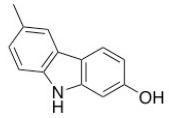

196.14
165.42
151.22
150.23
143.31
136.31
132.42
131.62
124.18
113.34
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.95
52.89
38.32
26.50
22.65
100 MHz 13C NMR Spectrum of Compound 28
(recorded in CDCl3)
CO2Me
O
O2N
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

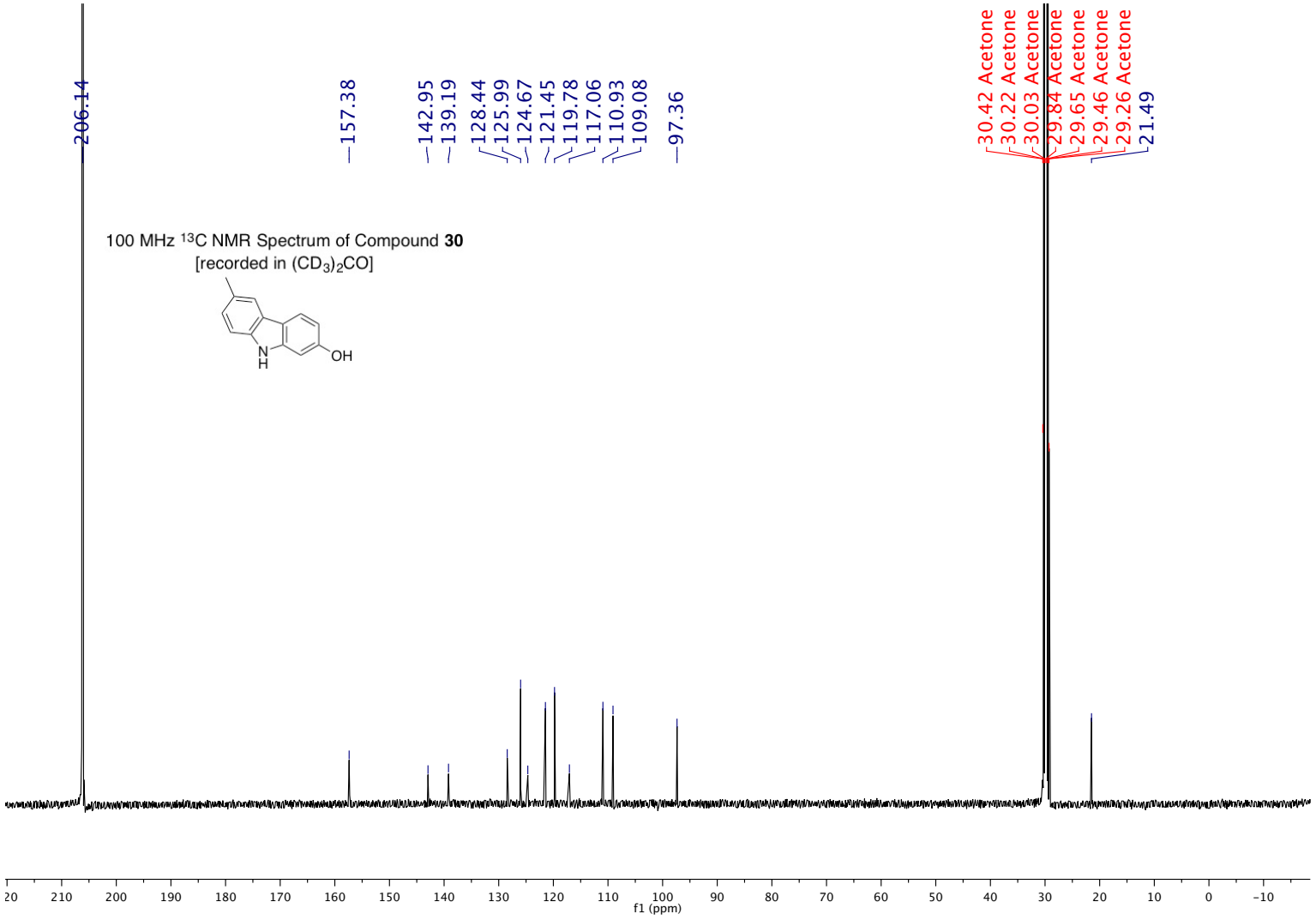
400 MHz ^{1}H NMR Spectrum of Compound **29**
[recorded in $(CD_3)_2CO$]



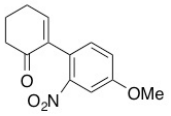

206.15
168.45
146.24
136.63
129.71
129.38
122.08
114.78
111.73
102.53
55.72
51.81
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.45 Acetone
29.26 Acetone
23.98
23.86
23.69
21.62
100 MHz ^{13}C NMR Spectrum of Compound **29**
[recorded in $(CD_3)_2CO$]
CO_2Me
OMe
23.98
23.86
23.69
24.2
24.0
23.8
23.6
23.4
f1 (ppm)
f1 (ppm)

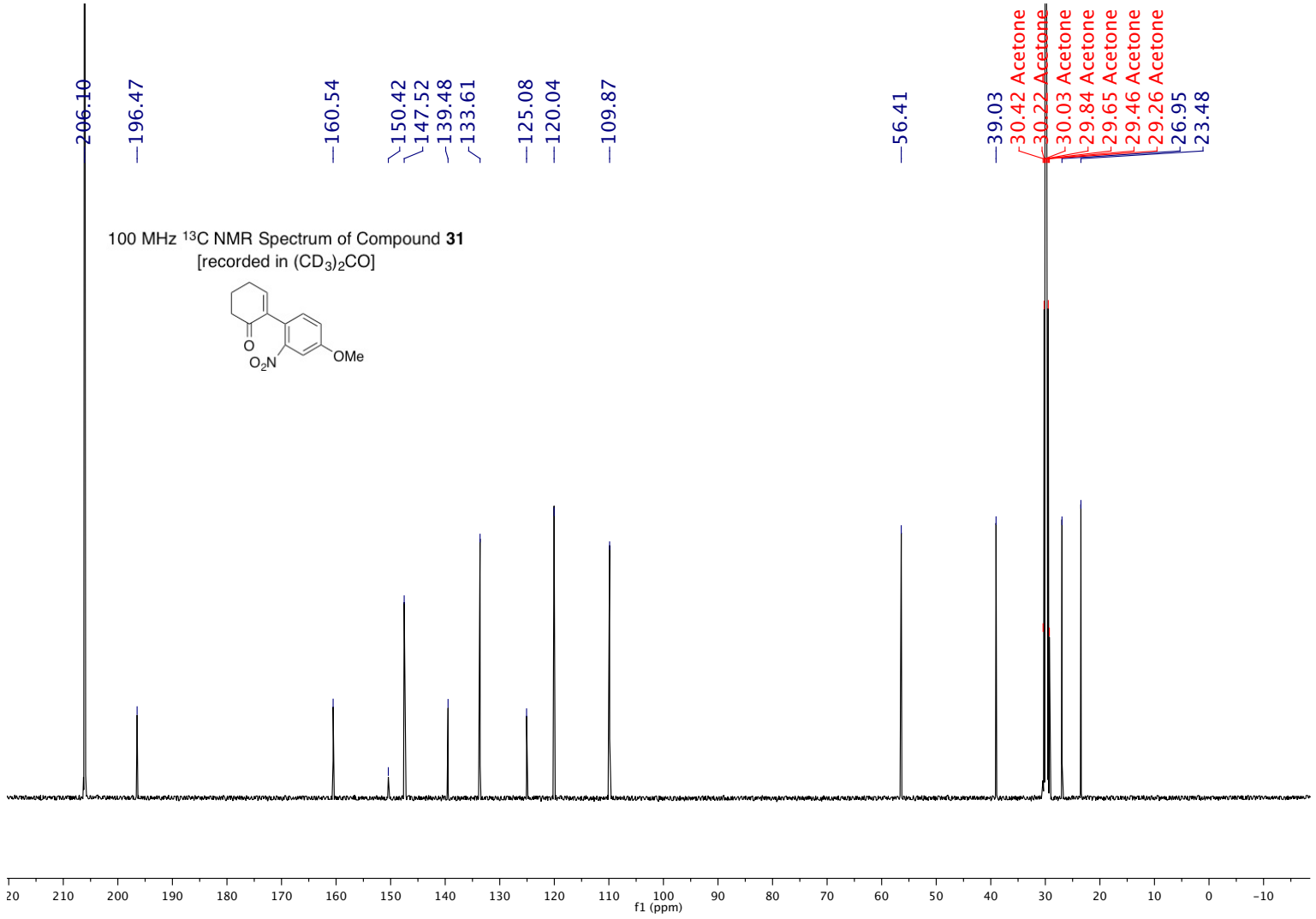
400 MHz ^{1}H NMR Spectrum of Compound **30**
[recorded in $(CD_3)_2CO$]



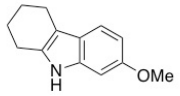

206.14
157.38
142.95
139.19
128.44
125.99
124.67
121.45
119.78
117.06
110.93
109.08
97.36
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
21.49
100 MHz ^{13}C NMR Spectrum of Compound **30**
[recorded in $(CD_3)_2CO$]
N
H
OH
f1 (ppm)

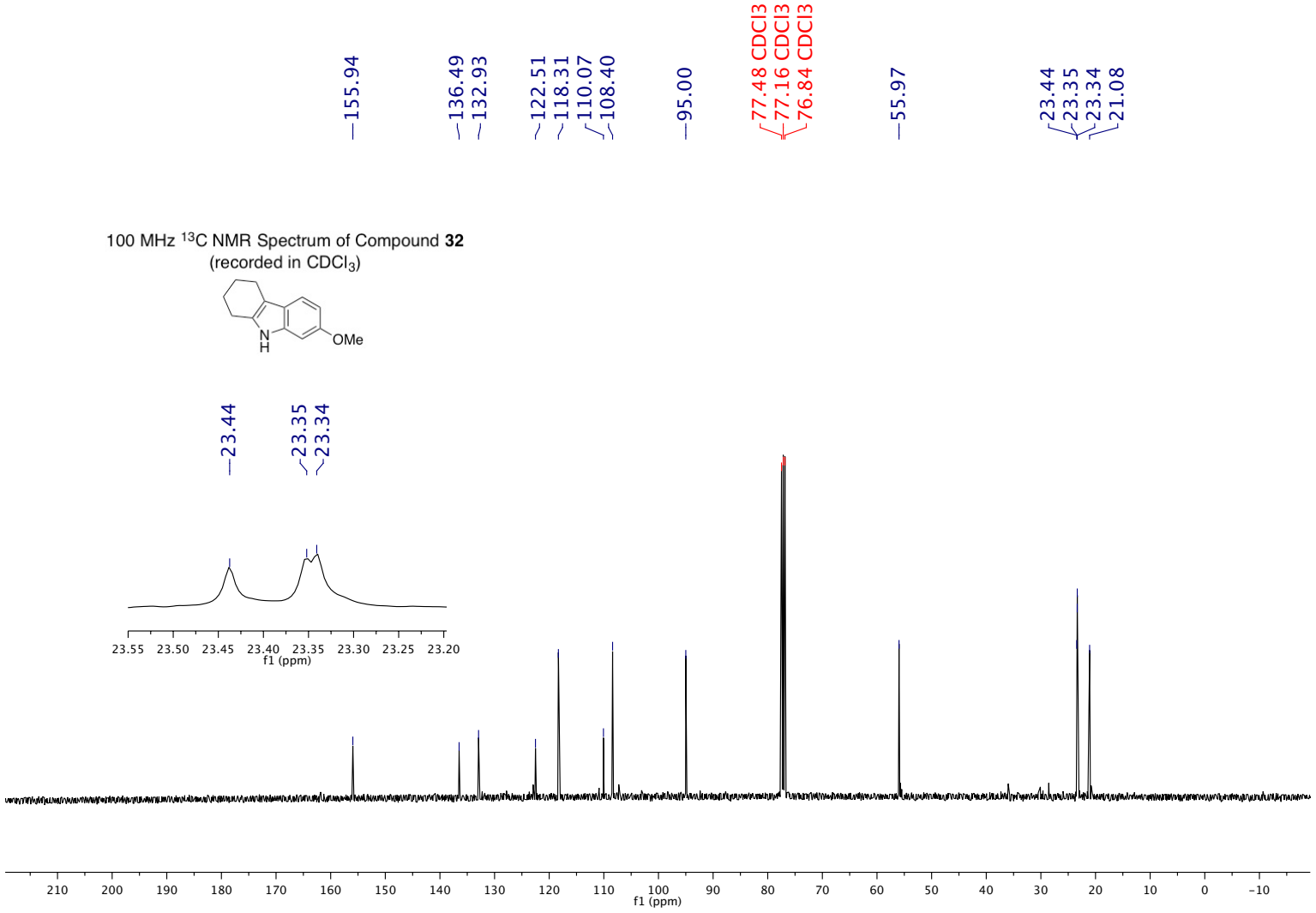
400 MHz ^{1}H NMR Spectrum of Compound **31**
[recorded in $(CD_3)_2CO$]




206.10
196.47
160.54
150.42
147.52
139.48
133.61
125.08
120.04
109.87
56.41
39.03
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
26.95
23.48
100 MHz ^{13}C NMR Spectrum of Compound **31**
[recorded in $(CD_3)_2CO$]
O
O_2N
OMe
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **32**
(recorded in $CDCl_3$)




155.94
136.49
132.93
122.51
118.31
110.07
108.40
95.00
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.97
23.44
23.35
23.34
21.08
100 MHz 13C NMR Spectrum of Compound 32
(recorded in CDCl3)
N
H
OMe
23.44
23.35
23.34
23.55 23.50 23.45 23.40 23.35 23.30 23.25 23.20
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Publication 2.

A Unified Approach to the Isomeric α-, β-, γ-, and δ-Carbolines via their 6,7,8,9-Tetrahydro Counterparts.

JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

A Unified Approach to the Isomeric α-, β-, γ-, and δ-Carbolines via their 6,7,8,9-Tetrahydro Counterparts

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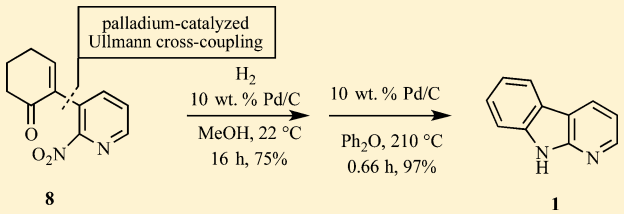
Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information

ABSTRACT: A cross-coupling/reductive cyclization protocol has been employed in a unified approach to all four carbolines. So, for example, the 2-nitropyridine **8**, which is readily prepared through an efficient palladium-catalyzed Ullmann cross-coupling reaction, is reductively cyclized under conventional conditions to give 6,7,8,9-tetrahydro-α-carboline that is itself readily aromatized to give α-carboline (**1**).



INTRODUCTION

The isomeric α-, β-, γ-, and δ-carbolines (**1**–**4**, respectively, in Figure 1) are important heterocyclic rings systems.[1] All are

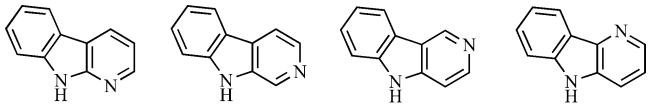


Figure 1. Isomeric α-, β-, γ-, and δ-carbolines (**1**–**4**).

found, albeit to varying extents, as key structural motifs in natural products. They also feature in a wide range of medicinally relevant compounds. The utility of their various derivatives in materials science is a further focus of current studies.[2] The α-carboline framework (**1**) is encountered in a limited number of naturally occurring anticancer agents and in the neuro-protective alkaloid mescengricin.[3] On the other hand, synthetically derived α-carbolines have shown anxiolytic, anti-inflammatory, central nervous system stimulating, and kinase inhibitory properties.[4] β-Carboline (**2**), itself a natural product isolated from both plants and micro-organisms, is the most well-known of the four systems and represents a key substructure associated with, for example, the eudistomine and manzamine classes of biologically active marine alkaloids.[5] Many medicinal agents embodying this heterocyclic framework have been identified.[5,6] Derivatives of γ-carboline (**3**) have been explored extensively as anticancer and anti-Alzheimer agents,[7] while those associated with δ-carboline (**4**) have been studied, inter alia, for their antibacterial and antitumor properties.[1b,8] δ-Carboline-containing alkaloids have been isolated from, for example, various West and Central African plants that are prized as sources of traditional medicines for treating malaria and certain infectious diseases.[1b]

A multitude of methods has been established for the synthesis of the carbolines, including classical ones involving Graebe–Ullmann, Fischer indolization, Bischler–Napieralski, and Pictet–Spengler reactions.[9,10] Variations on the Cadogan syntheses of carbazoles are also known,[11] as are routes involving the annulation of pyridines onto indoles,[9,10,12] including through Diels–Alder and electrocyclization processes. Generally speaking, though, "customized" approaches are required for the assembly of each of the α-, β-, γ-, and δ-carboline frameworks, thus prompting the search for more general routes to them.[13] There has been modest success in this regard, with the most effective route involving the cyclization of anilinopyridines.[13g–j] Recently, Driver[13i] and Ray[13j] have each reported variations on such methods that allow access to three of the four frameworks. It is against this background that we now detail a distinct, operationally simple, and likely flexible route to all four of the isomeric carbolines and highlight the utility of this through the synthesis of the simple natural product harman (**5**, Figure 2), a compound that displays anti-HIV and antibacterial properties.[14]

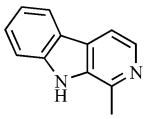


Figure 2. β-Carboline alkaloid harman (**5**).

RESULTS AND DISCUSSION

The pivotal steps associated with the unified approach to the carbolines reported here are the palladium-catalyzed Ullmann cross-coupling[15] of 2-iodocyclohex-2-en-1-one[16] with the relevant halogenated nitropyridine and the reductive cyclization of the ensuing 2-pyridylcyclohex-2-en-1-one to give the corresponding 6,7,8,9-tetrahydrocarboline. Oxidation of these tetrahydro compounds to their fully aromatic counterparts (viz., the carbolines) was readily accomplished using 10 wt % palladium on carbon. This sequence mirrors that used in our

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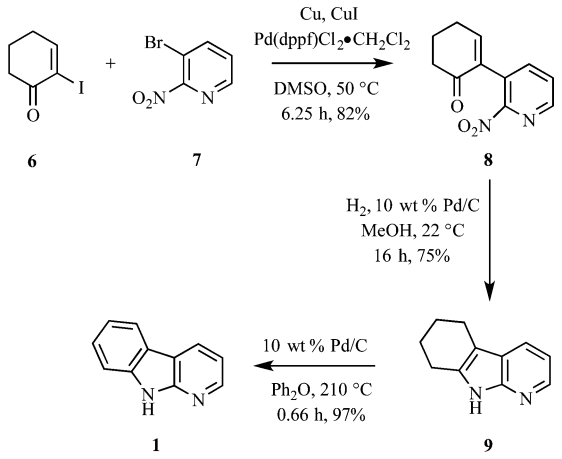
recently reported syntheses of various carbazole-based natural products, including glycoborine, glycozoline, clausazoline K, mukonine, and karapinchamine A.[17]

The synthesis of α-carboline (**1**), as shown in Scheme 1, is illustrative and starts with the palladium-catalyzed Ullmann

Scheme 1. Synthesis of α-Carboline (1)

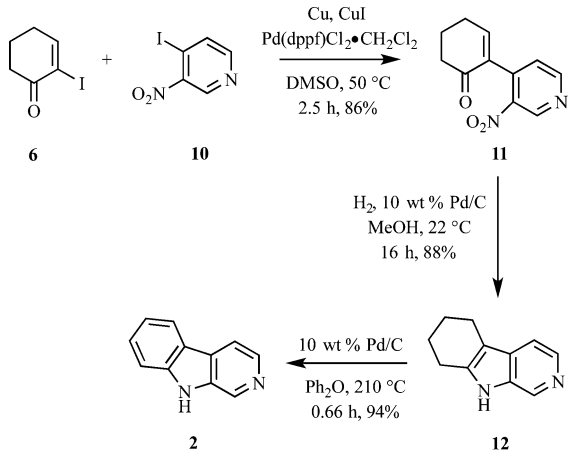


cross-coupling of the readily prepared[17] 2-iodocyclohex-2-en-1-one (**6**) with commercially available 3-bromo-2-nitropyridine (**7**), thus affording the 2-pyridylcyclohex-2-en-1-one (**8**) in 82% yield. In order to reduce the extent of homocoupling of the pyridine in this reaction, the iodo enone **6** was treated with a combination of copper metal, copper(I) iodide, and Pd(dppf)-Cl_2·CH_2Cl_2 in DMSO at 50 °C for 0.75 h prior the addition of compound **7**. Presumably this allows cupration of compound **6** to take place prior to a palladium-catalyzed cross-coupling reaction with halide **7**, thereby increasing the yields of product **8**. The reductive cyclization of compound **8** was effected using hydrogen in the presence of catalytic amounts of 10 wt % palladium on carbon (Pd/C) in methanol at room temperature for 16 h, and this produced the 6,7,8,9-tetrahydrocarboline (**9**)[18] in 75% yield. In our hands, the oxidation[19] of compound **9** to α-carboline (**1**)[4a] was best carried out by exposing the former system to an equivalent mass of 10 wt % palladium on carbon in diphenyl ether at 210 °C for 0.66 h. By such means target **1** was obtained in 97% yield, and all of the spectral data acquired on this material were in complete accord with the assigned structure and matched those reported in the literature. A single-crystal X-ray analysis was carried out on compound **1** and details of this are provided in the Experimental Section and the Supporting Information (SI).

Given the use of 10 wt % palladium on carbon in both the second and third steps of the reaction sequence, these could, in principle, be "telescoped" to establish a one-pot process. To date, however, we have not been able to identify conditions that allow for this to be conducted in both an operationally superior way and with better outcomes.

The synthesis of β-carboline (**2**) (Scheme 2) required 4-iodo-3-nitropyridine (**10**)[20] as a coupling partner, and this was readily obtained by reacting the commercially available chloro analogue with sodium iodide in acetonitrile (see the Experimental Section for details). Cross-coupling of compounds **6** and **10** proceeded smoothly under essentially the same conditions as employed for the conversion **6** + **7** → **8** and provided the anticipated coupling product **11** in 86% yield. Reductive cyclization of compound **11** proceeded uneventfully

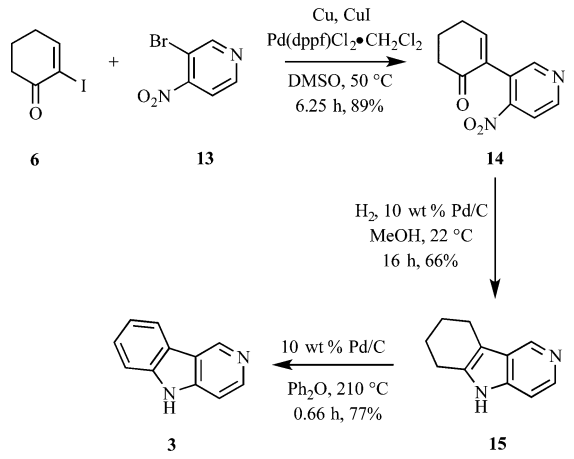
Scheme 2. Synthesis of β-Carboline (2)



under the previously established conditions, and product **12**[21] (88%) was readily oxidized to target **2** (94%) upon brief exposure to an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data acquired for β-carboline (**2**) matched those reported[22] previously. The structure of compound **2** was also confirmed by single-crystal X-ray analysis.

The analogous synthesis of γ-carboline (**3**) is shown in Scheme 3, and in this instance the required pyridine (**13**) was a

Scheme 3. Synthesis of γ-Carboline (3)



commercially available material. Reductive cyclization of the cross-coupling product **14** (89%) produced from compound **6** and **13** proceeded as anticipated to give the tetrahydrocarboline **15**,[23] albeit in just 66% yield. Similarly, the oxidation of this last compound under the previously employed conditions was less efficient than observed in the two previous cases, with compound **3**[24] being obtained in 77% yield. Once again, full characterization of this product was undertaken, including by single-crystal X-ray analysis.

The establishment of a unified approach to all the carbolines followed from the successful synthesis of δ-carboline (**4**) by the pathway shown in Scheme 4. So, as before, the palladium-catalyzed Ullmann cross-coupling of iodo enone **6** with the required and commercially available pyridine **16** proceeded uneventfully to give product **17** (75%) that was reductively cyclized in the usual manner to afford the tetrahydrocarboline **18**[25] (65%). Oxidation of this last compound using an equal

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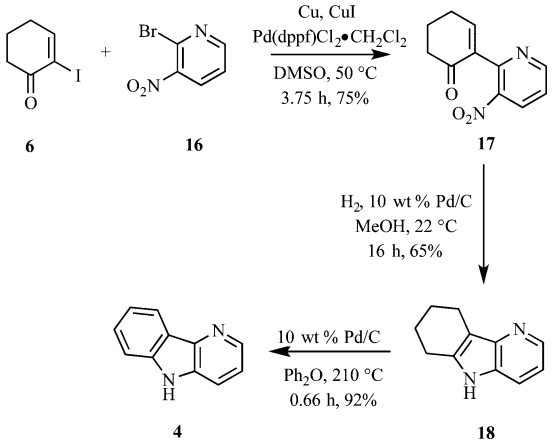
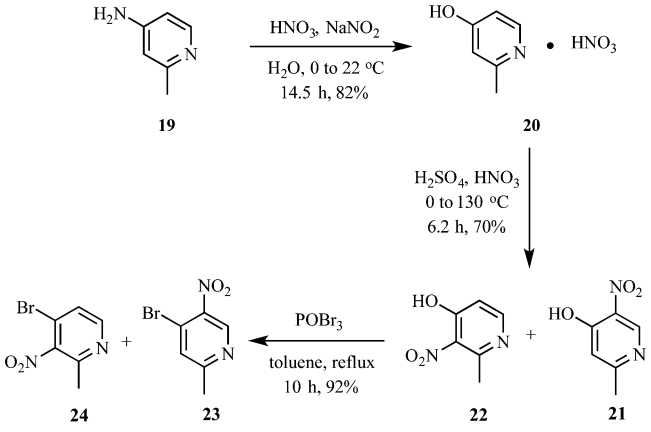
Scheme 4. Synthesis of δ-Carboline (4)



mass of 10 wt % palladium on carbon in hot diphenyl ether then gave δ-carboline (**4**)[26] (92%) that was subject to the usual range of spectroscopic analyses, including a single-crystal X-ray study.

In order to test the capacities of the above-mentioned protocols to deliver substituted carbolines, the β-carboline-based natural product harman (**5**, Figure 2) was targeted for synthesis. The required pyridine was prepared by the route shown in Scheme 5. Thus, commercially available 2-

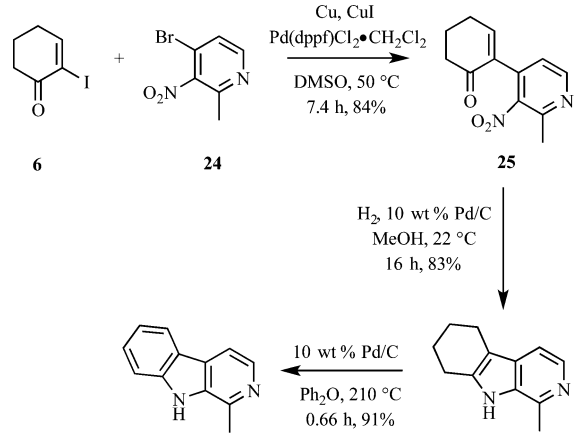
Scheme 5. Route to the Trisubstituted Pyridine 24 Required for the Synthesis of the β-Carboline Alkaloid Harman (5)



methylpyridin-4-amine (**19**) was subjected to a Sandmeyer reaction using water as the nucleophile, thus providing the previously reported nitric acid salt[27] **20** of 2-methylpyridin-4-ol. Aromatic nitration of this last compound could only be achieved under rather forcing conditions, thus providing a 1:3 and inseparable mixture of pyridines **21** and **22** (70% combined yield). Accordingly, this mixture was treated with $POBr_3$ in refluxing toluene, thereby affording what is presumed to be the corresponding mixture of bromides **23** and **24** (92% combined yield). These regioisomers could only be separated by HPLC techniques but sufficient quantities of the pure form of the latter could be accumulated by such means. The former product (presumed to be compound **23**) was not purified or subject to any spectroscopic characterization.

With compound **24** in hand, the synthesis of harman (**5**) was completed by the now standard pathway shown in Scheme 6. Thus, palladium-catalyzed Ullmann cross-coupling of iodo

Scheme 6. Completion of the Synthesis of Harman (5)



enone **6** with pyridine **24** delivered the required product **25** in 84% yield. Reductive cyclization of the last compound under the usual conditions gave tetrahydroharman **26**[28] (83%), which could be oxidized to the natural product **5**[14,29] (91%) on treatment with an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data, including those derived from a single-crystal X-ray analysis, acquired for compound **5** confirmed the assigned structure, and appropriate comparisons with those reported[14] for the natural product were entirely favorable.

CONCLUSIONS

The reaction sequences reported here should allow for the rational/logical design of pathways to a wide range of α-, β-, γ-, and δ-carbolines. This is all the more so given the increasingly ready availability of a wide range of polysubstituted pyridines[30] and 2-iodocyclohex-2-en-1-ones. For similar reasons, the protocols defined here should allow for ready access to a wide range of azaindoles, compounds of considerable interest from a medicinal chemistry perspective.[31] Studies exploiting such possibilities will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral], where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (νmax) as thin films on KBr plates. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double-focusing, triple-sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in positive ion mode. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concd)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid

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(concd)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[32] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. The copper powder used in the palladium-catalyzed Ullmann cross-coupling reactions had a particle size of <75 μm. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[33] Where necessary, reactions were performed under a nitrogen atmosphere by subjecting the relevant solution to reduced pressure for several minutes and then admitting nitrogen. This process was repeated three times.

Specific Chemical Transformations. *2-(2-Nitropyridin-3-yl)-cyclohex-2-en-1-one (**8**).* A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**)[16] (2.63 g, 11.82 mmol), copper powder (1.50 g, 23.65 mmol), CuI (1.69 g, 8.87 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (483 mg, 0.59 mmol) in degassed DMSO (118 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time, a solution of commercially available 3-bromo-2-nitropyridine (**7**) (1.20 g, 5.91 mmol) in degassed DMSO (30 mL) was added to the reaction mixture over 1.5 h. After a further 4 h, the reaction mixture was cooled, quenched with water (30 mL), and then diluted with ethyl acetate (50 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 50 mL), and the separated organic phase associated with the combined filtrates was washed with water (2 × 100 mL) and then brine (2 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:11 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40−60 petroleum ether), compound **8** (1.06 g, 82%) as a light-brown solid: mp = 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 4.7 and 1.7 Hz, 1H), 7.74 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.60 (dd, *J* = 7.6 and 4.7 Hz, 1H), 7.08 (t, *J* = 4.2 Hz, 1H), 2.60 (m, 4H), 2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 157.0, 148.5, 147.8, 141.7, 137.2, 128.1, 126.7, 38.2, 26.5, 22.6; IR ν_{max} 2950, 1679, 1540, 1405, 1366, 975, 864, 810, 707 cm^{-1}; MS (ESI, +ve) *m*/*z* 241 [$(M + Na)^+$, 100%]; HRMS *m*/*z* $(M + Na)^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0591.

*6,7,8,9-Tetrahydro-5H-pyrido[2,3-b]indole (**9**).* A magnetically stirred mixture of compound **8** (30 mg, 0.14 mmol) and 10 wt % Pd/C (12 mg) in degassed methanol (7 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C and then filtered, and the solids thus retained were washed with methanol (20 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.7 in ethyl acetate) then gave compound **9**[18] (18 mg, 75%) as a white, crystalline solid: mp = 155−156 °C (lit.[18] mp = 155−156 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (m, 1H), 8.19 (d, *J* = 4.3 Hz, 1H), 7.75 (dd, *J* = 7.7 and 1.3 Hz, 1H), 7.01 (dd, *J* = 7.7 and 4.3 Hz, 1H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.70 (m, 2H), 1.98−1.86 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 140.8, 135.4, 125.7, 120.8, 115.1, 108.4, 23.3(4), 23.2(8), 23.1, 20.8; IR ν_{max} 3149, 3075, 2921, 2846, 1587, 1418, 1289, 786, 765, 677 cm^{-1}; MS (ESI, +ve) *m*/*z* 173 [$(M + H)^+$, 100%]; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

*9H-Pyrido[2,3-b]indole (α-Carboline, **1**).* A magnetically stirred mixture of compound **9** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids so retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/40−60 petroleum ether gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40−60 petroleum ether) gave compound **1**[4a] (19 mg, 97%) as a white, crystalline solid: mp = 200−202 °C (lit.[4a] mp = 215−217 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 7.7 and 1.5 Hz, 1H), 8.34 (dd, *J* = 4.9 and 1.2 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.48−7.44 (complex m, 1H), 7.26−7.19 (complex m, 2H) (signal due to N−H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 152.9, 146.1, 140.6, 129.9, 128.0, 122.0, 121.9, 121.0, 118.0, 116.1, 112.3; IR ν_{max} 3048, 2984, 2906, 1600, 1587, 1572, 1455, 1411, 1274, 998, 767, 736 cm^{-1}; MS (ESI, +ve) *m*/*z* 169 [$(M + H)^+$, 100%]; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0768.

*4-Iodo-3-nitropyridine (**10**).* A magnetically stirred solution of commercially available 4-chloro-3-nitropyridine (1.00 g, 6.31 mmol) in acetonitrile (126 mL) maintained at ambient temperatures was treated with sodium iodide (17.02 g, 113.55 mmol). The ensuing mixture was heated under reflux for 2 h and then cooled to 22 °C and diluted with ethyl acetate (200 mL). The resulting solution was washed with Na_2CO_3 (1 × 100 mL of a saturated aqueous solution), Na_2SO_3 (1 × 50 mL of a saturated solution), water (1 × 200 mL), and brine (1 × 100 mL) before being dried (Na_2SO_4,), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 twice in 1:5 v/v ethyl acetate/40−60 petroleum ether), 4-iodo-3-nitropyridine (**10**)[20] (1.46 g, 92%) as a light-yellow solid: mp = 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (broad s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 8.03 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 149.6, 145.9, 136.5, 98.5; IR ν_{max} 1572, 1540, 1521, 1357, 1223, 1058, 835, 657 cm^{-1}; MS (EI, 70 eV) *m*/*z* 250 ($M^{+\bullet}$, 100%), 204 (70), 177 (60); HRMS *m*/*z* $M^{+\bullet}$ calcd for $C_5H_3{}^{127}IN_2O_2$ 249.9239, found 249.9236.

*2-(3-Nitropyridin-4-yl)cyclohex-2-en-1-one (**11**).* A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (888 mg, 4.00 mmol), copper powder (508 mg, 8.00 mmol), CuI (571 mg, 3.00 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (163 mg, 0.20 mmol) in degassed DMSO (40 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of compound **10** (500 mg, 2.00 mmol) in degassed DMSO (10 mL) was added to the reaction mixture over 1 h. After a further 0.75 h, the reaction mixture was cooled, quenched with water (10 mL), and then diluted with ethyl acetate (15 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 15 mL), and the separated organic phase associated with the combined filtrates was washed with water (2 × 30 mL) and then brine (2 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. This was subjected to flash column chromatography (silica, 1:3:10 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) and gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:1 v/v ethyl acetate/40−60 petroleum ether], compound **11** (374 mg, 86%) as a light-yellow solid: mp = 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.78 (d, *J* = 4.9 Hz, 1H), 7.22 (d, *J* = 4.9 Hz, 1H), 7.13 (t, *J* = 4.2 Hz, 1H), 2.63−2.57 (complex m, 4H), 2.19−2.13 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 153.9, 148.7, 145.3, 145.0, 140.0, 137.5, 125.6, 38.2, 26.5, 22.5; IR ν_{max} 2948, 1679, 1600, 1542, 1523, 1357, 1217, 1159, 1121, 851, 716 cm^{-1}; MS (ESI, +ve) *m*/*z* 219 [$(M + H)^+$, 100%]; HRMS *m*/*z* $(M + H)^+$ calcd for $C_{11}H_{11}N_2O_3$ 219.0770, found 219.0768.

*6,7,8,9-Tetrahydro-5H-pyrido[3,4-b]indole (**12**).* A magnetically stirred mixture of compound **11** (190 mg, 0.87 mmol) and 10 wt % Pd/C (76 mg) in degassed methanol (44 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C and then filtered, and the solids thus retained were washed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure, and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after

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concentration of the appropriate fractions [R_f = 0.3(5) in 1:1 v/v methanol/dichloromethane], compound **12**[21] (132 mg, 88%) as a white, crystalline solid: mp = 163−164 °C (lit.[21] mp = 199−200 °C); ^{1}H NMR (700 MHz, CD_3OD) δ 8.49 (broad s, 1H), 7.97 (broad s, 1H), 7.36 (d, J = 4.9 Hz, 1H), 2.77 (t, J = 6.0 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.92−1.83 (complex m, 4H) (signal due to N−H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 142.2, 136.9, 134.5, 134.2, 132.6, 113.7, 110.4, 24.2(2), 24.2(0), 24.0, 21.6; IR ν_{max} 3143, 3040, 2926, 2850, 2839, 1569, 1471, 1442, 1359, 1142, 1030, 808 cm^{-1}; MS (ESI, +ve) m/z 173 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

*9H-Pyrido[3,4-b]indole (β-Carboline, **2**).* A magnetically stirred mixture of compound **12** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids so retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:1 v/v ethyl acetate/40−60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:2 v/v methanol/dichloromethane), compound **2**[22] (18 mg, 94%) as a white, crystalline solid: mp = 210−211 °C (lit.[22] mp = 199−201 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.27 (d, J = 5.3 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.56 (m, 2H), 7.29−7.23 (complex m, 1H) (signal due to N−H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 138.4, 137.8, 134.1, 130.4, 129.7, 122.7, 122.2, 120.8, 116.1, 112.8; IR ν_{max} 3134, 3052, 2963, 2754, 1628, 1449, 1331, 1245, 746, 732 cm^{-1}; MS (ESI, +ve) m/z 191 [(M + Na)$^+$, 70%], 169 [(M + H)$^+$, 100]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0766.

*2-(4-Nitropyridin-3-yl)cyclohex-2-en-1-one (**14**).* A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (2.19 g, 9.85 mmol), copper powder (1.26 g, 19.70 mmol), CuI (1.41 g, 7.39 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (400 mg, 0.49 mmol) in degassed DMSO (98 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time, a solution of compound **13** (1.00 g, 4.93 mmol) in degassed DMSO (25 mL) was added to the reaction mixture over 1.5 h. After a further 4 h, the reaction mixture was cooled, quenched with water (20 mL), and then diluted with ethyl acetate (1 × 30 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 30 mL), and the separated organic phase associated with the combined filtrates was washed with water (2 × 60 mL) and then brine (2 × 60 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:11 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 1:3:6 v/v/v acetone/dichloromethane/40−60 petroleum ether), compound **14** (956 mg, 89%) as a light-brown solid: mp = 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 5.3 Hz, 1H), 8.61 (s, 1H), 7.81 (d, J = 5.3 Hz, 1H), 7.17 (t, J = 4.2 Hz, 1H), 2.66−2.58 (complex m, 4H), 2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 154.1, 152.8, 151.4, 148.6, 136.0, 125.4, 116.6, 38.2, 26.5, 22.6; IR ν_{max} 2945, 1677, 1557, 1529, 1401, 1358, 1222, 1159, 839, 705, 675 cm^{-1}; MS (ESI, +ve) m/z 241 [(M + Na)$^+$, 100%], 219 [(M + H)$^+$, 15]; HRMS m/z (M + Na)$^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0589.

*6,7,8,9-Tetrahydro-5H-pyrido[4,3-b]indole (**15**).* A magnetically stirred mixture of compound **14** (50 mg, 0.23 mmol) and 10 wt % Pd/C (20 mg) in degassed methanol (12 mL) was maintained under an atmosphere of hydrogen at 22 °C for 16 h and then filtered, and the solids so retained were washed with methanol (25 mL). The combined filtrates were concentrated under reduced pressure, and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions [R_f = 0.3(5) in 1:1 v/v methanol/dichloromethane], compound **15**[23] (26 mg, 66%) as a white, crystalline solid: mp = 223−224 °C (lit.[23] mp = 269−271 °C); ^{1}H NMR (700 MHz, CD_3OD) δ 8.58 (broad s, 1H), 8.05 (broad s, 1H), 7.28 (d, J = 5.3 Hz, 1H), 2.74 (m, 4H), 1.95−1.87 (complex m, 4H) (signal due to N−H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 141.6, 139.9, 139.1, 138.1, 126.2, 110.3, 107.5, 24.2, 24.1, 23.9, 21.6; IR ν_{max} 2926, 2839, 2693, 1625, 1466, 1294, 1169, 1142, 989, 802, 684 cm^{-1}; MS (ESI, +ve) m/z 173 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

*5H-Pyrido[4,3-b]indole (γ-Carboline, **3**).* A magnetically stirred mixture of compound **15** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 40−60 petroleum ether elution → 1:3 v/v methanol/dichloromethane gradient elution) to give, after concentration of the appropriate fractions [R_f = 0.2(5) in 1:3 v/v methanol/dichloromethane], compound **3**[24] (15 mg, 77%) as a white, crystalline solid: mp = 223−225 °C (lit.[24] mp = 225−227 °C); ^{1}H NMR [700 MHz, $(CD_3)_2SO$] δ 11.69 (s, 1H), 9.33 (s, 1H), 8.43 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.56 (m, 1H), 7.47 (m, 2H), 7.26 (t, J = 7.4 Hz, 1H); ^{13}C NMR [175 MHz, $(CD_3)_2SO$] δ 144.5, 143.5, 142.7, 139.5, 126.5, 120.7, 120.6, 119.9, 119.4, 111.4, 106.4; ^{1}H NMR (700 MHz, CD_3OD) δ 9.20 (s, 1H), 8.36 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.49−7.46 (m, 2H), 7.28 (t, J = 7.4 Hz, 1H) (signal due to N−H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 145.8, 144.4, 142.7, 141.5, 128.2, 122.4, 121.6(4), 121.6(0), 121.5, 112.4, 107.6; IR ν_{max} 3062, 2956, 2806, 2679, 1607, 1582, 1467, 1239, 999, 744 cm^{-1}; MS (ESI, +ve) m/z 169 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0766.

*2-(3-Nitropyridin-2-yl)cyclohex-2-en-1-one (**17**).* A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (1.09 g, 4.93 mmol), copper powder (630 mg, 9.85 mmol), CuI (704 mg, 3.69 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (200 mg, 0.25 mmol) in degassed DMSO (50 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time, a solution of compound **16** (500 mg, 4.93 mmol) in degassed DMSO (12 mL) was added to the reaction mixture over 1 h. After a further 2 h, the reaction mixture was cooled, quenched with water (10 mL), diluted with ethyl acetate (15 mL), and then filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 15 mL), and the separated organic phase associated with the combined filtrates was washed with water (2 × 30 mL) and then brine (2 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:12 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:3:6 v/v/v acetone/dichloromethane/40−60 petroleum ether], compound **17** (403 mg, 75%) as a light-brown solid: mp = 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, J = 4.7 and 1.3 Hz, 1H), 8.29 (dd, J = 8.2 and 1.3 Hz, 1H), 7.49−7.43 (complex m, 2H), 2.65 (m, 2H), 2.58 (m, 2H), 2.20−2.13 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 152.9, 151.0, 149.4, 146.1, 139.2, 132.2, 123.4, 38.3, 26.6, 22.5; IR ν_{max} 2947, 1677, 1593, 1561, 1526, 1451, 1357, 765 cm^{-1}; MS (ESI, +ve) m/z 241 [(M + Na)$^+$, 100%], 219 [(M + H)$^+$, 15]; HRMS m/z (M + Na)$^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0589.

*6,7,8,9-Tetrahydro-5H-pyrido[3,2-b]indole (**18**).* A magnetically stirred mixture of compound **17** (213 mg, 0.98 mmol) and 10 wt % Pd/C (86 mg) in degassed methanol (49 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C and then filtered, and the solids so retained were washed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure, and the white solid thus obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40−60 petroleum ether), compound **18**[25] (109 mg, 65%) as a white, crystalline solid: mp = 183−185 °C (lit.[25] mp = 200−202 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (broad s, 1H), 8.38 (d, J

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= 4.3 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.00 (m, 1H), 2.84 (m, 2H), 2.76 (m, 2H), 1.95−1.84 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 141.9, 139.2, 129.1, 117.4, 115.8, 110.8, 23.8, 23.2, 23.1, 20.1; IR ν_{max} 3136, 3083, 3053, 2929, 2847, 1483, 1414, 1362, 1286, 1144, 904, 767, 729 cm^{-1}; MS (ESI, +ve) m/z 173 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1080.

5H-Pyrido[3,2-b]indole (δ-Carboline, 4). A magnetically stirred mixture of compound **18** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/40−60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions [R_f = 0.2(5) in 1:1 v/v ethyl acetate/40−60 petroleum ether], compound **4**[26] (18 mg, 92%) as a white, crystalline solid: mp = 211−212 °C (lit.[26] mp = 206−207 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (dd, J = 4.8 and 1.4 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.52 (m, 2H), 7.40 (m, 1H), 7.26 (m, 1H) (signal due to N−H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 142.4, 142.3, 141.5, 135.1, 129.0, 122.4, 121.4, 121.3, 120.8, 119.9, 112.6; IR ν_{max} 3057, 2979, 2919, 2848, 2760, 1629, 1460, 1396, 1320, 1223, 741, 724 cm^{-1}; MS (ESI, +ve) m/z 169 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0766.

2-Methylpyridin-4-ol Nitrate (20). Commercially available 2-methylpyridin-4-amine (8.00 g, 73.98 mmol) was dissolved in a mixture of concentrated HNO_3 (44.1 mL) and H_2O (59.4 mL), and the resulting solution was cooled, with vigorous magnetic stirring, to 0 °C. A chilled solution of $NaNO_2$ (7.40 g, 107.25 mmol) in water (21.7 mL) was then added dropwise over 0.5 h, and the mixture thus formed stirred at 0 °C for 4 h before being allowed to warm to 22 °C and then stirred at this temperature for another 10 h and was recooled to 0 °C. The resulting solid was removed by filtration, the filtrate was concentrated to about one-third of its original volume and then cooled to 0 °C, and a second crop of solid was removed by filtration. The combined solids were then air-dried to give the nitric acid salt[27] of compound **20** (10.49 g, 82%) as a white, crystalline solid: mp = 162−164 °C (lit.[27] mp = 164−165 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 6.5 Hz, 1H), 7.11−7.09 (complex m, 2H), 2.62 (s, 3H) (signals due to O−H and N−H group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4, 156.0, 143.2, 114.7, 113.0, 19.3; IR ν_{max} 3098, 2919, 2617, 1627, 1501, 1305, 1216, 830 cm^{-1}; MS (ESI, +ve) m/z 110 [(M + H)$^+$, 100%]; HRMS m/z (M + H)$^+$ calcd for C_6H_8NO 110.0606, found 110.0608.

2-Methyl-4-nitropyridin-3-ol (21) and 2-Methyl-3-nitropyridin-4-ol (22). A magnetically stirred solution of salt **20** (3.00 g, 17.43 mmol) in concentrated H_2SO_4 (6.9 mL) was cooled to 0 °C and then treated, dropwise, with fuming HNO_3 (6.9 mL). The ensuing mixture was stirred at 0 °C for 0.17 h, heated at 130 °C for 20 h, and then cooled to 0 °C and carefully neutralized with NaOH (25 mL of a 10 M aqueous solution). FC-grade silica gel (20 g) was added to the ensuing mixture, and this was then concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v methanol/dichloromethane), a 1:3 mixture of 2-methyl-5-nitropyridin-4-ol (**21**) and 2-methyl-3-nitropyridin-4-ol (**22**) (1.88 g, 70% combined yield) as a white crystalline solid: mp = 148−150 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (major product) 12.17 (broad s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ (for mixture) 168.2, 151.2, 148.1, 143.5, 142.2, 139.4, 137.8, 137.3, 120.7, 118.0, 18.2, 15.3; IR ν_{max} 3037, 2796, 1612, 1557, 1502, 1356, 1222, 836, 768 cm^{-1}; MS (ESI, +ve) m/z 331 (42%), 177 [(M + Na)$^+$, 100], 155 [(M + H)$^+$, 10]; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_6H_6N_2NaO_3$ 177.0276, found 177.0278.

4-Bromo-2-methyl-3-nitropyridine (24). A magnetically stirred 1:3 mixture of 2-methyl-5-nitropyridin-4-ol (**21**) and 2-methyl-3-nitropyridin-4-ol (**22**) (1.12 g, 7.27 mmol), obtained as described immediately above, in toluene (8.0 mL) and maintained under a nitrogen atmosphere was treated with $POBr_3$ (2.19 g, 7.63 mmol). The ensuing mixture was heated under reflux for 10 h and then cooled to 0 °C before being quenched with NaOH (30 mL of a 1 M aqueous solution). The ensuing mixture was extracted with ethyl acetate (1 × 150 mL) and washed with H_2O (2 × 150 mL). The separated organic phase was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solid so obtained was subjected to flash column chromatography (silica, 1:3:20 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 1:3:6 v/v/v acetone/dichloromethane/40−60 petroleum ether), a 1:3 mixture of what is presumed to be 4-bromo-2-methyl-5-nitropyridine (**23**) and 4-bromo-2-methyl-3-nitropyridine (**24**) (1.46 g, 92% combined) as a white solid. A ca. 800 mg portion of this material was subjected to semipreparative HPLC (silica, normal phase, 17:83 v/v ethyl acetate/*n*-hexane elution, 600 mL/h) to afford, after concentration of the relevant fractions (R_t = 0.45 h), a pure sample of 4-bromo-2-methyl-3-nitropyridine (**24**) (ca. 350 mg) as a white, crystalline solid: mp = 78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 5.3 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.5, 148.5, 126.3, 123.7, 20.9; IR ν_{max} 3072, 1575, 1534, 1365, 1266, 846, 837, 714 cm^{-1}; MS (EI, 70 eV) m/z 218 and 216 (M$^{+\bullet}$, both 90%), 201 and 199 (both 70), 172 and 170 (both 95), 93 and 91 (both 83), 62 (100%); HRMS m/z M$^{+\bullet}$ calcd for $C_6H_5{}^{79}BrN_2O_2$ 215.9534, found. 215.9533.

2-(2-Methyl-3-nitropyridin-4-yl)cyclohex-2-en-1-one (25). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (205 mg, 0.92 mmol), copper powder (117 mg, 1.84 mmol), CuI (132 mg, 0.69 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (38 mg, 0.05 mmol) in degassed DMSO (9 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time, a solution of compound **24** (100 mg, 0.46 mmol) in degassed DMSO (3 mL) was added to the reaction mixture over 0.66 h. After a further 6 h the reaction mixture was cooled, quenched with water (3 mL), and then diluted with ethyl acetate (5 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel, and the solids so retained were rinsed with ethyl acetate (2 × 5 mL). The separated organic phase associated with the combined filtrates was washed with water (2 × 10 mL) and then brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 3:9:40 v/v/v acetone/dichloromethane/40−60 petroleum ether elution) gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:3:6 v/v/v acetone/dichloromethane/40−60 petroleum ether], compound **25** (90 mg, 84%) as a light-brown, crystalline solid: mp = 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 5.0 Hz, 1H), 7.09−7.05 (complex m, 2H), 2.66 (s, 3H), 2.58−2.54 (complex m, 4H), 2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 151.4, 150.8, 150.1, 146.6, 139.0, 136.3, 123.4, 38.2, 26.5, 22.5, 22.0; IR ν_{max} 2939, 1681, 1594, 1528, 1359, 1229, 860 cm^{-1}; MS (ESI, +ve) m/z 255 [(M + Na)$^+$, 100%], 233 [(M + H)$^+$, 10]; HRMS m/z (M + Na)$^+$ calcd for $C_{12}H_{12}N_2NaO_3$ 255.0746, found 255.0734.

1-Methyl-6,7,8,9-tetrahydro-5H-pyrido[3,4-b]indole (26). A magnetically stirred mixture of compound **25** (103 mg, 0.44 mmol) and 10 wt % Pd/C (42 mg) in degassed methanol (22 mL) was maintained under an atmosphere of hydrogen at 22 °C for 16 h and then filtered, and the solids thus retained were washed with methanol (50 mL). The combined filtrates were concentrated under reduced pressure, and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v methanol/dichloromethane), compound **26**[28] (69 mg, 83%) as a white, crystalline solid: mp = 187−189 °C (lit.[28] mp = 184−188 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, J = 5.4 Hz, 1H), 7.19 (d, J = 5.4 Hz, 1H), 2.78 (broad s, 2H), 2.63 (broad s, 5H), 1.91−1.84 (complex m, 4H) (signal due to N−H group proton not observed);

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^{13}C NMR (100 MHz, CD_3OD) δ 141.6, 141.2, 136.7, 133.7, 132.9, 111.9, 110.6, 24.3, 24.2, 24.1, 21.7, 19.1; IR ν_{max} 3045, 2930, 2846, 1563, 1498, 1308, 1226, 809 cm^{-1}; MS (ESI, +ve) m/z 187 [$(M + H)^+$, 100%]; HRMS m/z $(M + H)^+$ calcd for $C_{12}H_{15}N_2$ 187.1235, found 187.1232.

*1-Methyl-9H-pyrido[3,4-b]indole (Harman, **5**).* A magnetically stirred mixture of compound **26** (36 mg, 0.19 mmol) and 10 wt % Pd/C (36 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids so retained were washed with ethyl acetate (2 × 7 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 40−60 petroleum ether elution →1:9 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:3 v/v methanol/dichloromethane), compound **5**[29] (32 mg, 91%) as a white, crystalline solid: mp = 233−235 °C (lit.[29] mp = 235−238 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (broad s, 1H), 8.38 (d, J = 5.4 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 5.4 Hz, 1H), 7.56−7.51 (complex m, 2H), 7.29 (m, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.3, 138.7, 134.8, 128.5, 128.4, 122.2, 122.0, 120.2, 113.1, 111.7, 20.5; IR ν_{max} 3135, 3068, 2925, 1626, 1568, 1504, 1450, 1323, 1251, 1237, 742 cm^{-1}; MS (ESI, +ve) m/z 183 [$(M + H)^+$, 100%]; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{12}H_{11}N_2$ 183.0922, found 183.0922.

X-ray Crystallographic Studies. *Crystallographic Data. Compound 1.* $C_{11}H_8N_2$, M = 168.20, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 11.1814(2) Å, b = 5.53776(8) Å, c = 13.4546(2) Å, β = 96.2939(15)°, V = 828.09(2) Å^3, D_x = 1.349 g cm^{-3}, 1673 unique reflections ($2\theta_{max}$ = 147.6°), R = 0.035 [for 1520 reflections with $I > 2.0\sigma(I)$], Rw = 0.089 (all data), S = 1.00.

Compound 2. $C_{11}H_8N_2$, M = 168.20, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.8440(1) Å, b = 9.8140(1) Å, c = 14.4195(1) Å, V = 827.00(2) Å^3, D_x = 1.351 g cm^{-3}, 1004 unique reflections ($2\theta_{max}$ = 147.8°), R = 0.027 [for 998 reflections with $I > 2.0\sigma(I)$], Rw = 0.073 (all data), S = 1.00.

Compound 3. $C_{11}H_8N_2$, M = 168.20, T = 150 K, orthorhombic, space group $Pna2_1$, Z = 4, a = 17.1576(6) Å, b = 12.2955(6) Å, c = 3.8213(2) Å, V = 806.15(6) Å^3, D_x = 1.386 g cm^{-3}, 944 unique reflections ($2\theta_{max}$ = 147.8°), R = 0.032 [for 906 reflections with $I > 2.0\sigma(I)$], Rw = 0.062 (all data), S = 1.00.

Compound 4. $C_{11}H_8N_2$, M = 168.20, T = 150 K, monoclinic, space group Ia, Z = 4, a = 12.1155(7) Å, b = 3.9036(2) Å, c = 18.1199(13) Å, β = 107.250(7)°, V = 818.42(9) Å^3, D_x = 1.365 g cm^{-3}, 820 unique reflections ($2\theta_{max}$ = 146.6°), R = 0.042 [for 807 reflections with $I > 2.0\sigma(I)$], Rw = 0.107 (all data), S = 1.05.

Compound 5. $C_{12}H_{10}N_2$, M = 182.23, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 8, a = 9.5865(2) Å, b = 13.2423(4) Å, c = 15.1680(4) Å, V = 1925.54(9) Å^3, D_x = 1.257 g cm^{-3}, 1994 unique reflections ($2\theta_{max}$ = 52.0°), R = 0.032 [for 1805 reflections with $I > 2.0\sigma(I)$], Rw = 0.073 (all data), S = 1.00.

Structure Determination. Images for compound **5** were collected on a diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) fitted with an area detector, and the data were extracted using CrysAlis PRO.[34] Images for compounds **1**, **2**, **3**, and **4** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector, and the data were extracted using the CrysAlis PRO.[34] The structure solutions for all 5 compounds were solved by direct methods (SIR92)[35] and then refined using the CRYSTALS program package.[36] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1530002, 1530003, 1530004, 1530005, 1530006). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre (12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00323.

Crystallographic data for **1** in CIF format (CIF)
Crystallographic data for **2** in CIF format (CIF)
Crystallographic data for **3** in CIF format (CIF)
Crystallographic data for **4** in CIF format (CIF)
Crystallographic data for **5** in CIF format (CIF)
ORTEPs derived from the single-crystal X-ray analyses of compounds **1**−**5** and ^{1}H and ^{13}C NMR spectra of compounds **1**−**5**, **8**−**12**, **14**, **15**, **17**, **18**, **20**, **21**/**22**, and **24**−**26** (PDF)

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Notes

The authors declare no competing financial interest.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1530002, 1530003, 1530004, 1530005, 1530006). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre at 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 1223 336033).

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SUPPORTING INFORMATION FOR:

A Unified Approach to the Isomeric α-, β-, γ- and δ-Carbolines via their 6,7,8,9-Tetrahydro-counterparts

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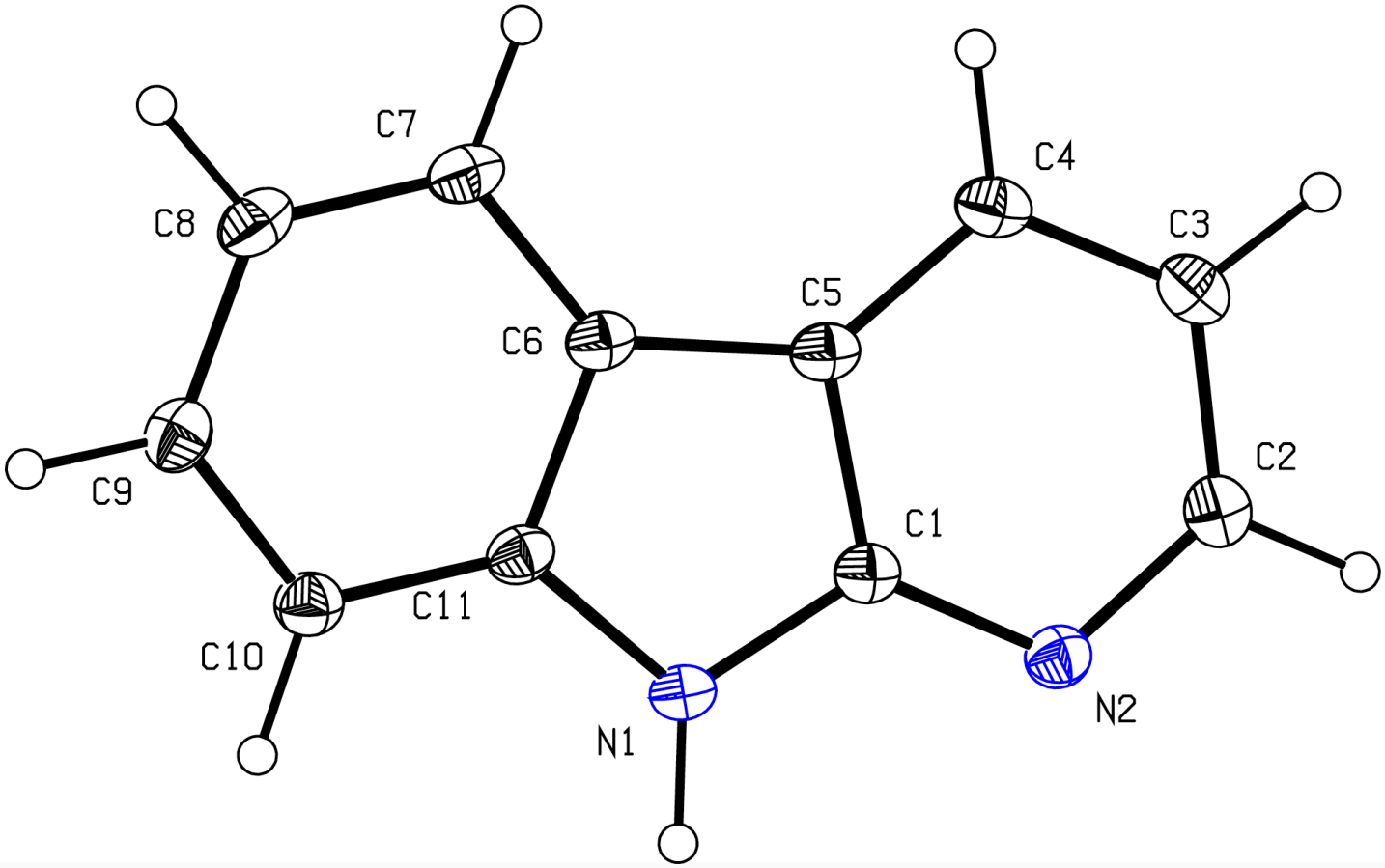


Figure S1: Structure of compound **1** (CCDC 1530002) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

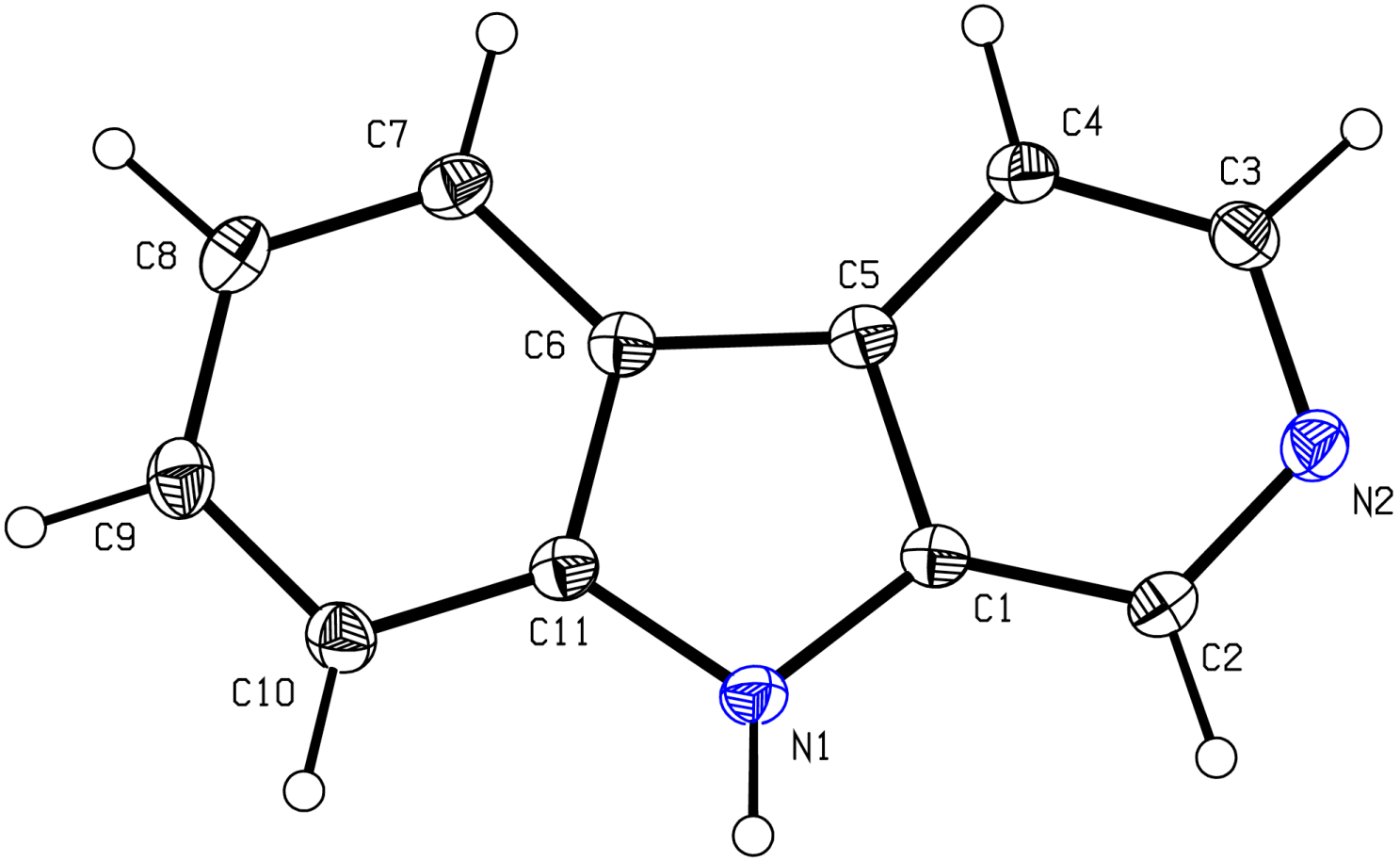


Figure S2: Structure of compound **2** (CCDC 11530003) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

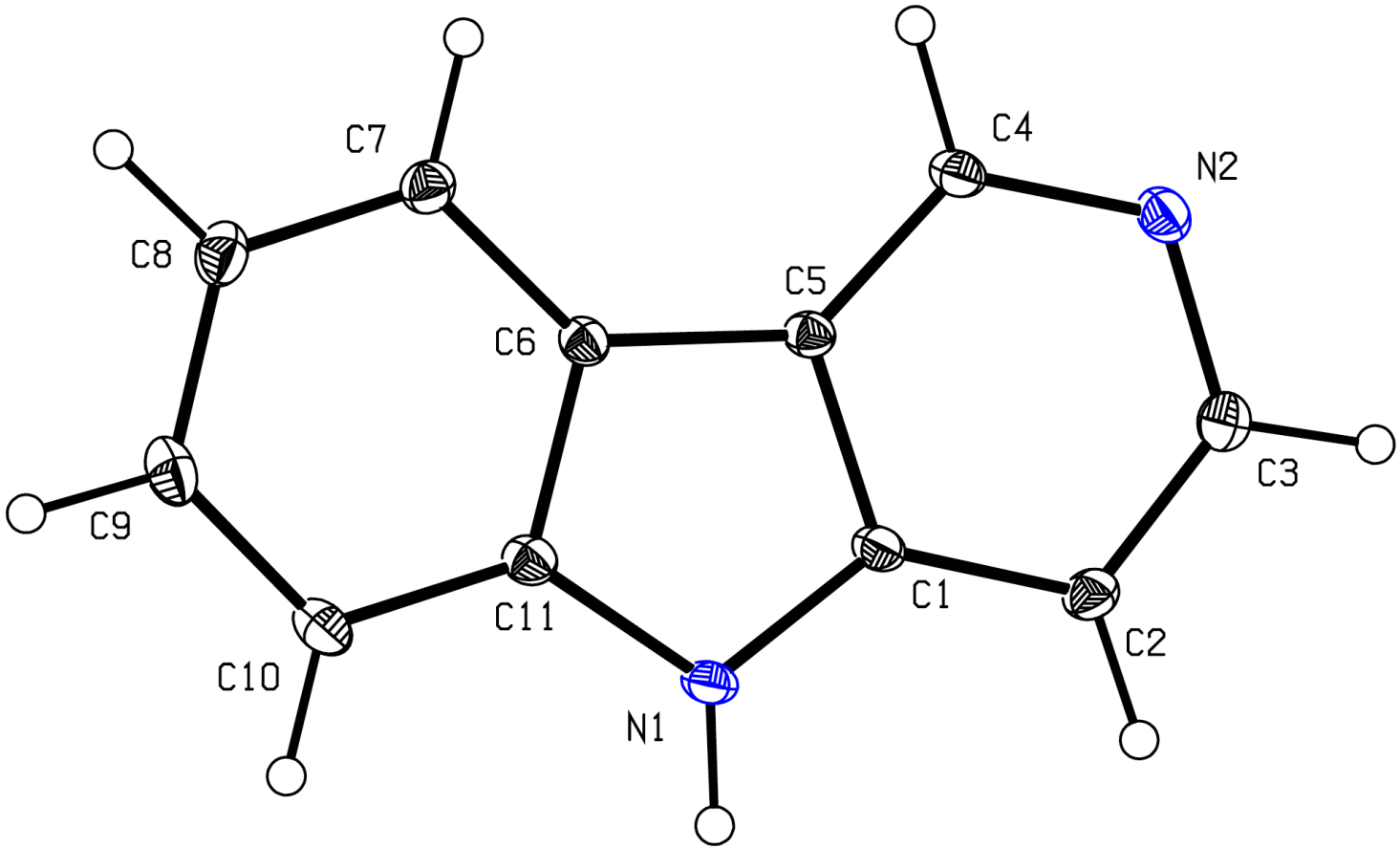


Figure S3: Structure of compound **3** (CCDC 1530004) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

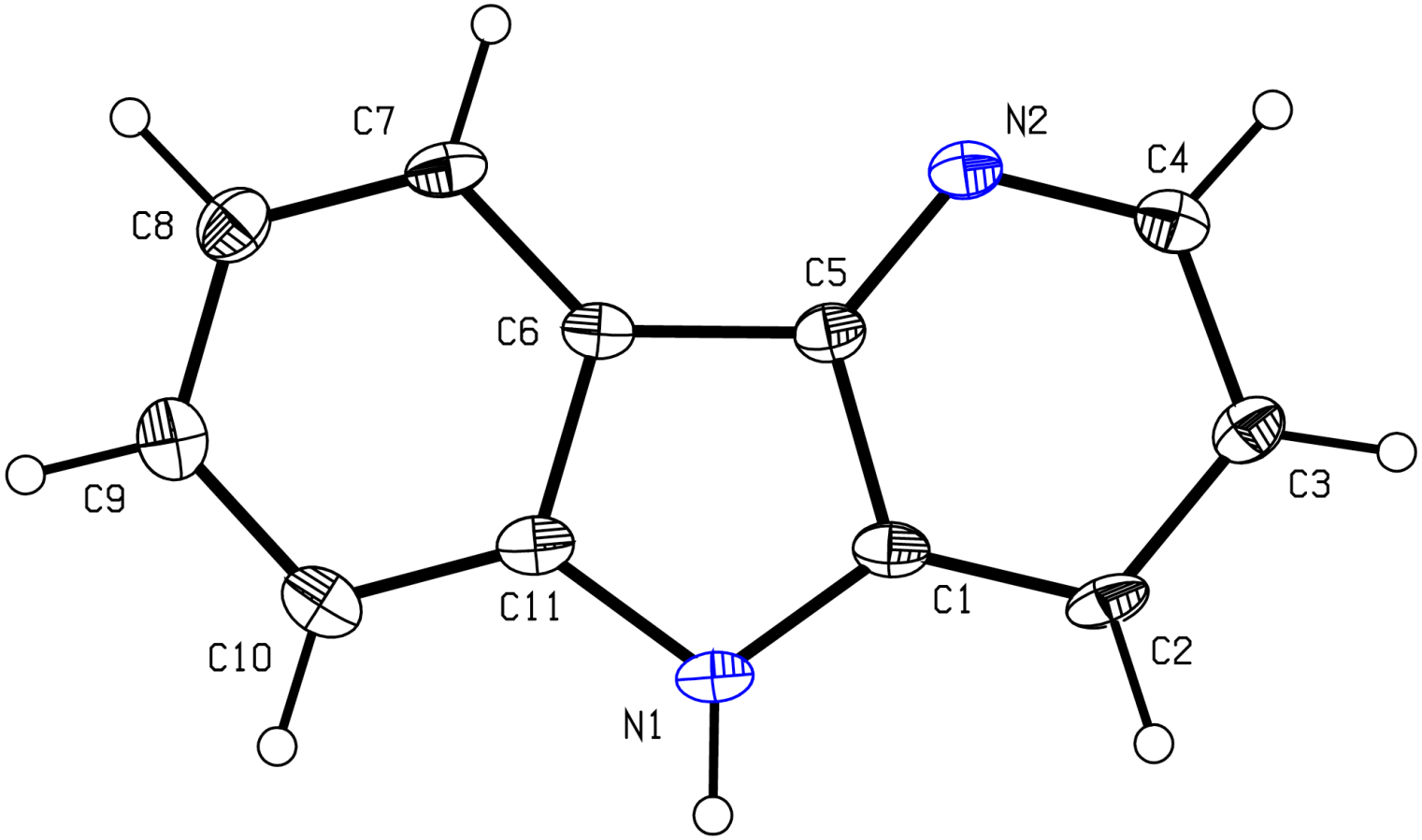


Figure S4: Structure of compound **4** (CCDC 1530005) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

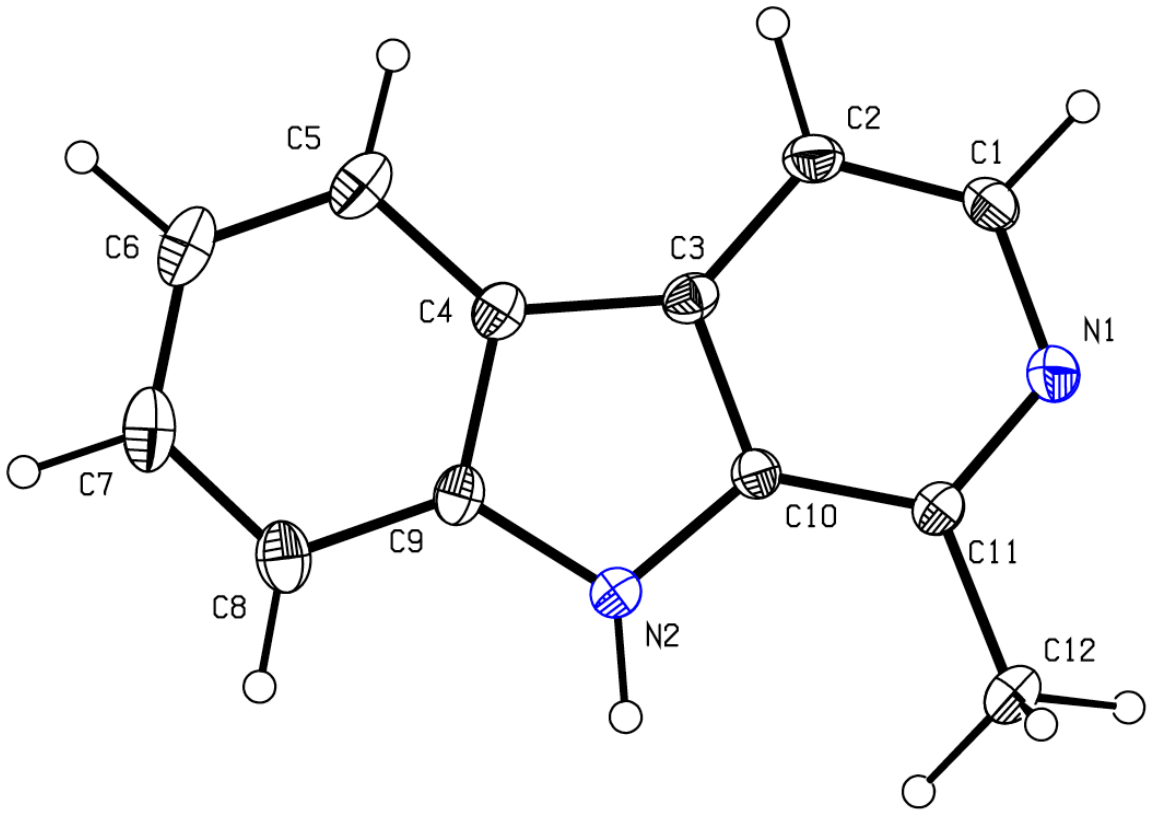
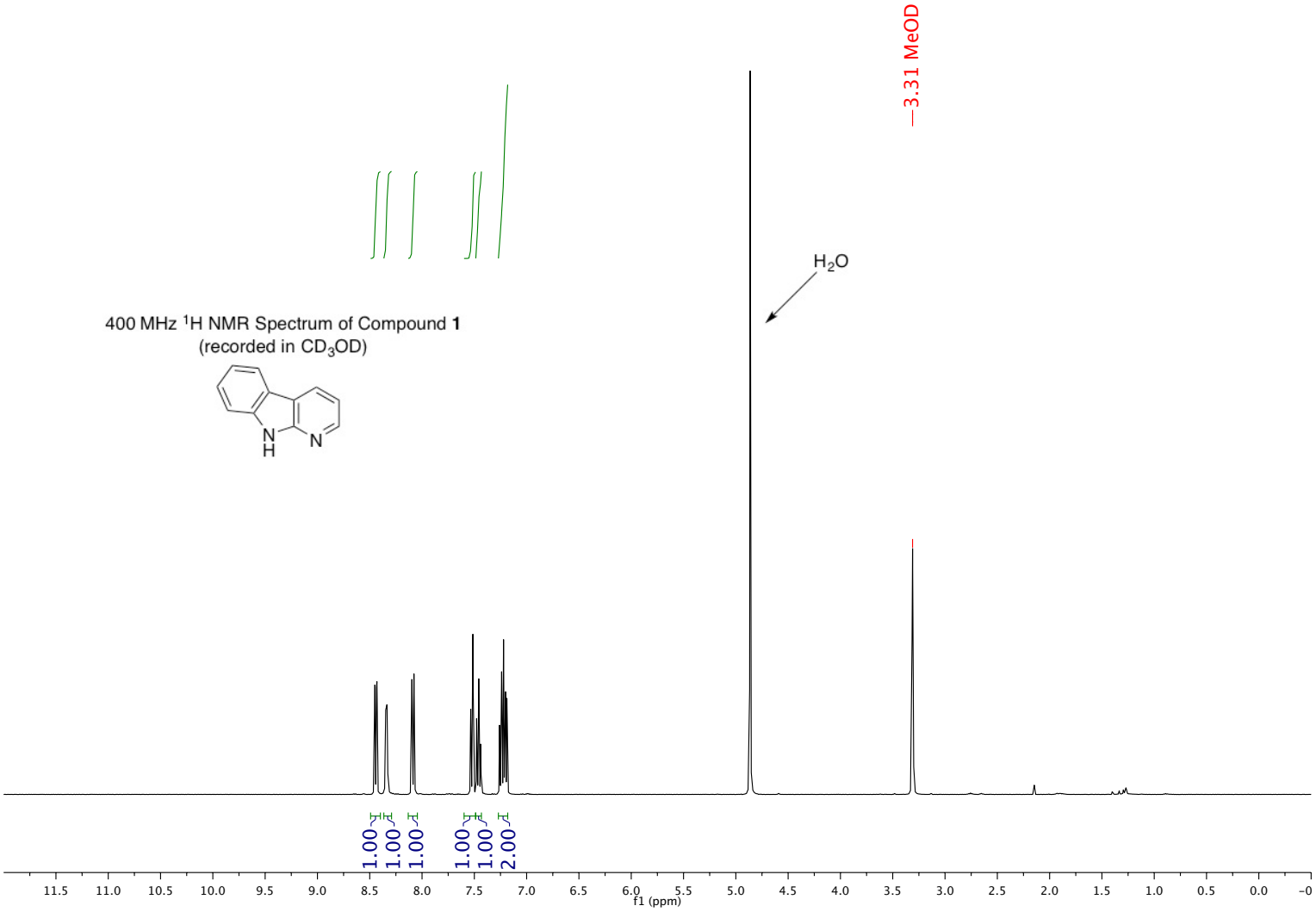
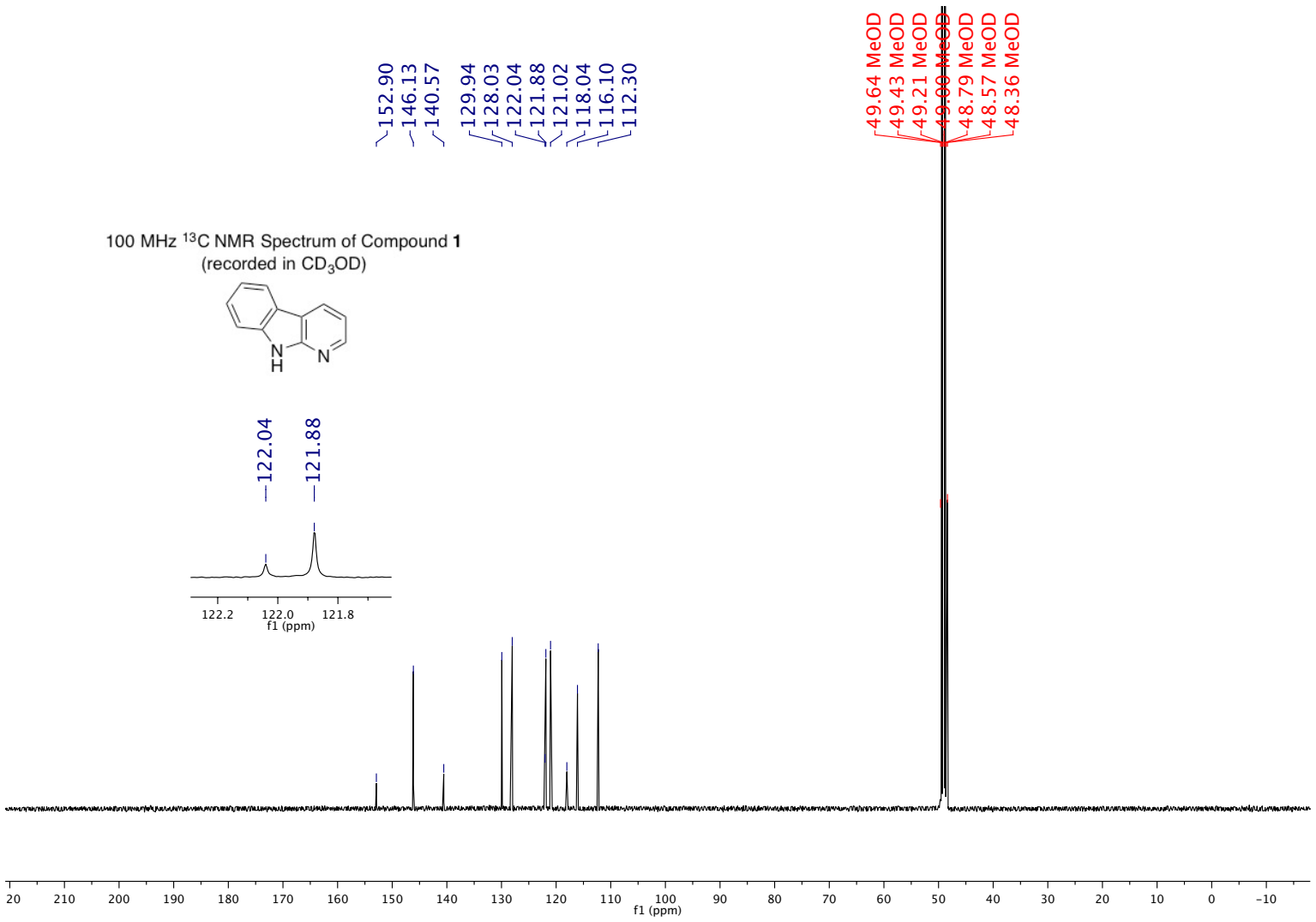
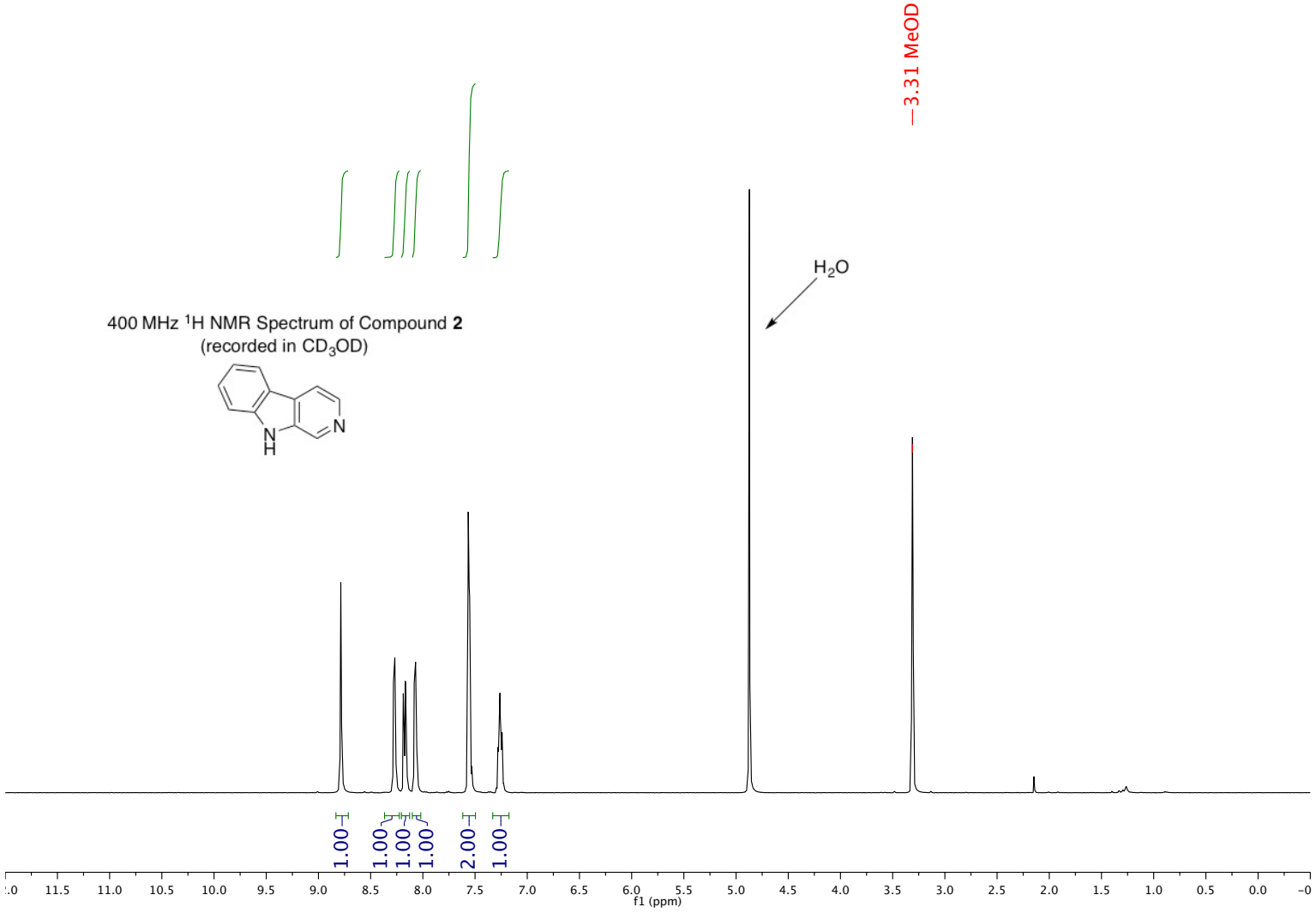
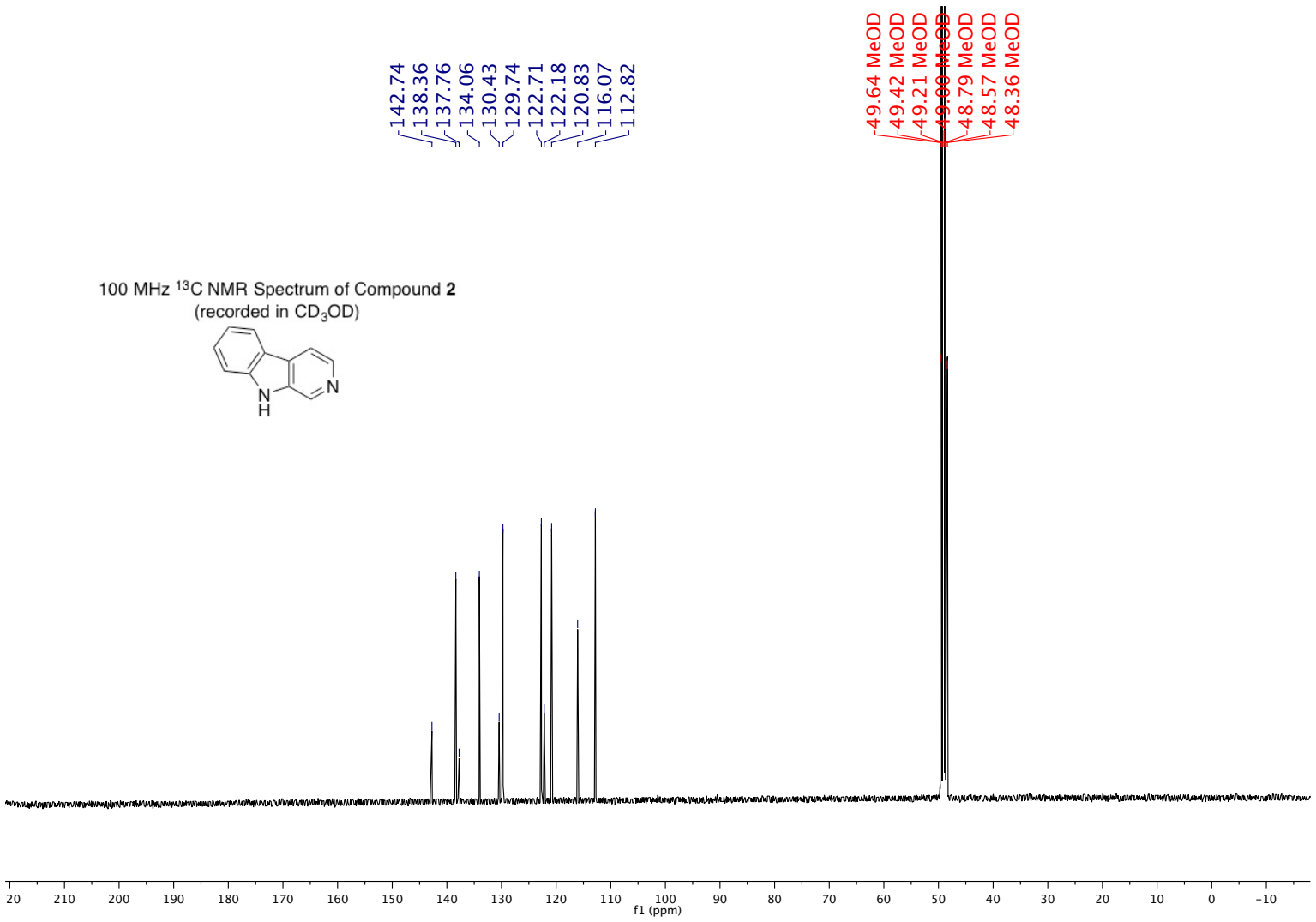


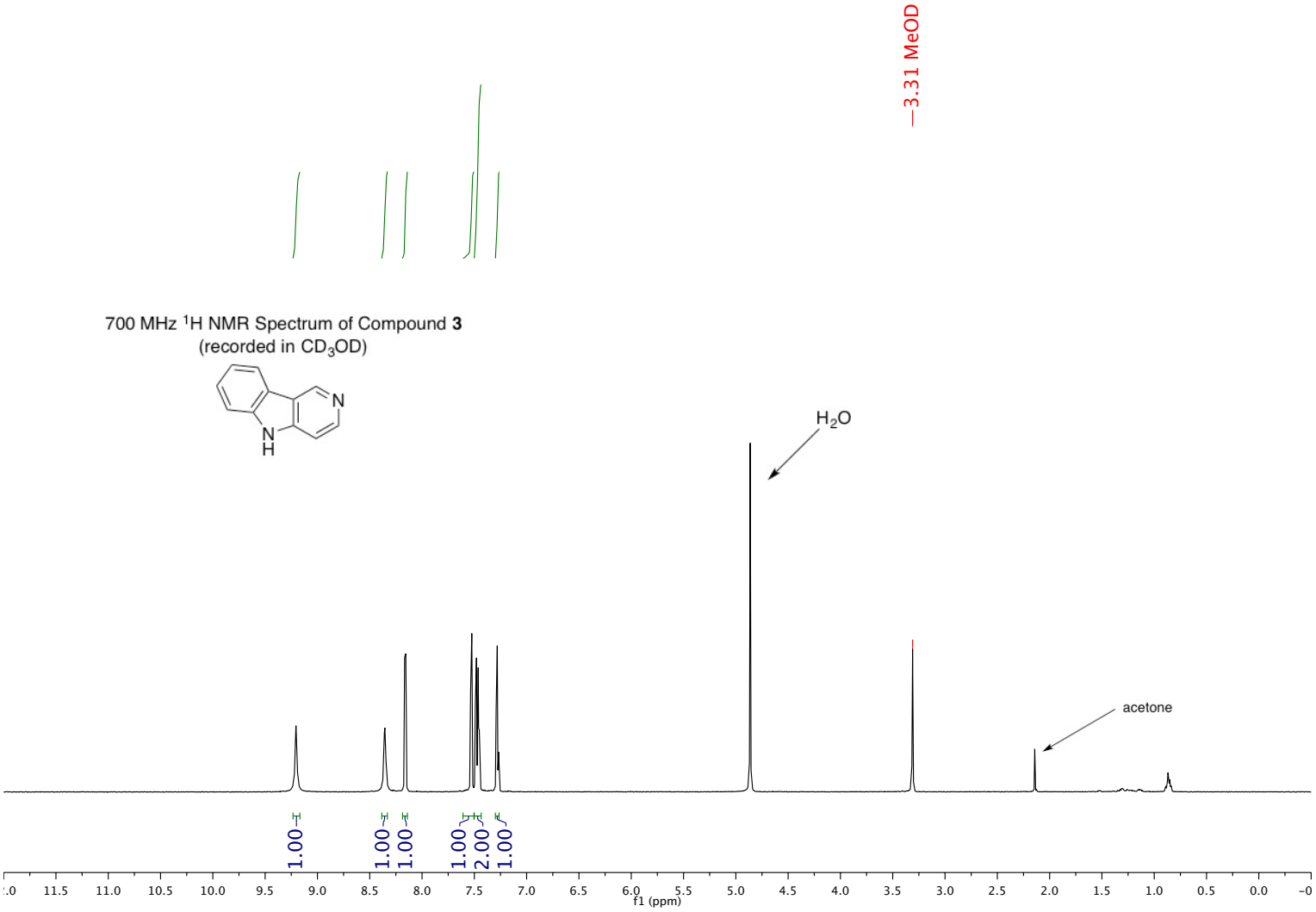
Figure S5: Structure of compound **5** (CCDC 1530006) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

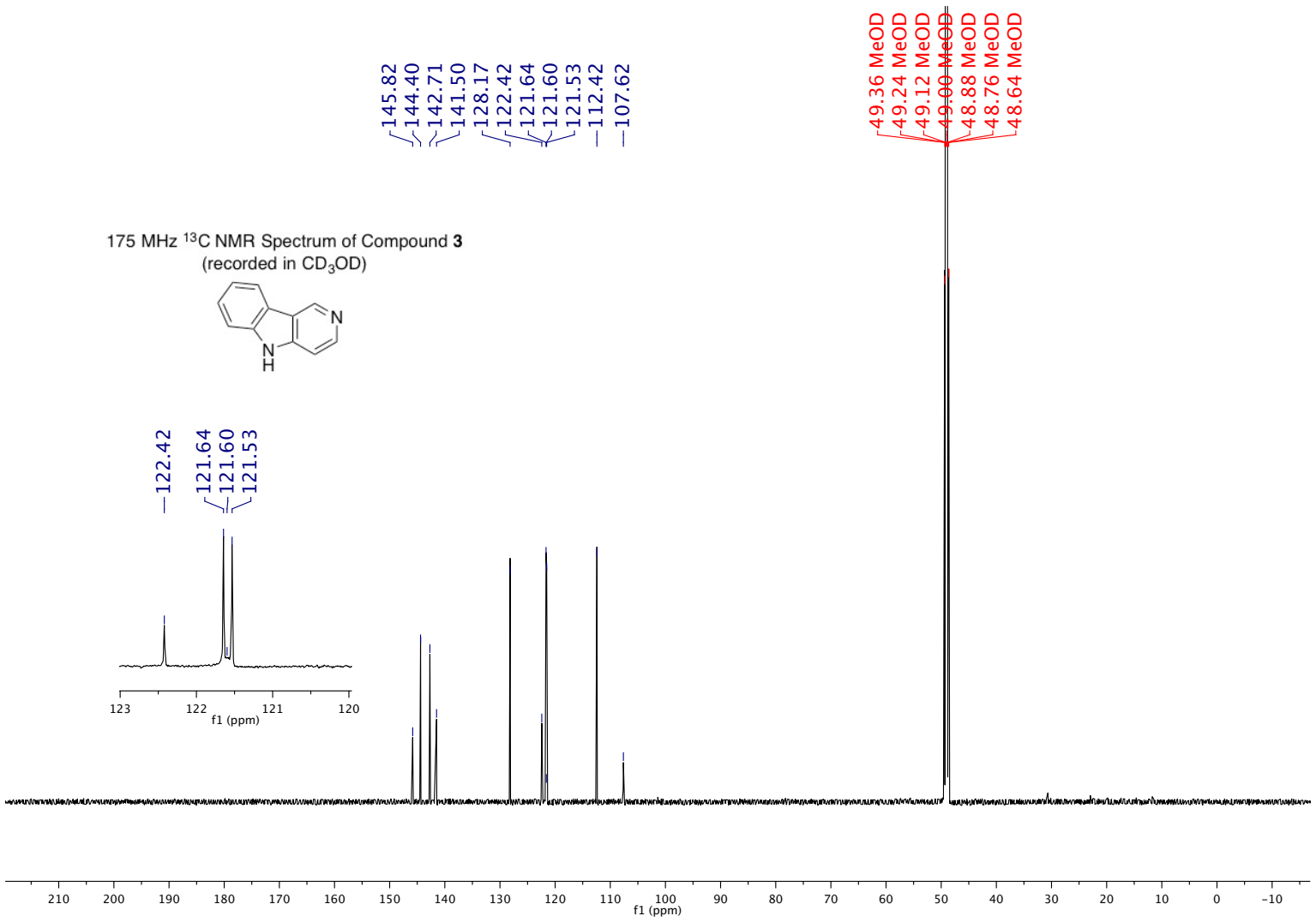

400 MHz ^{1}H NMR Spectrum of Compound **1**
(recorded in CD_3OD)
N
H
N
3.31 MeOD
H_2O
1.00
1.00
1.00
1.00
1.00
2.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

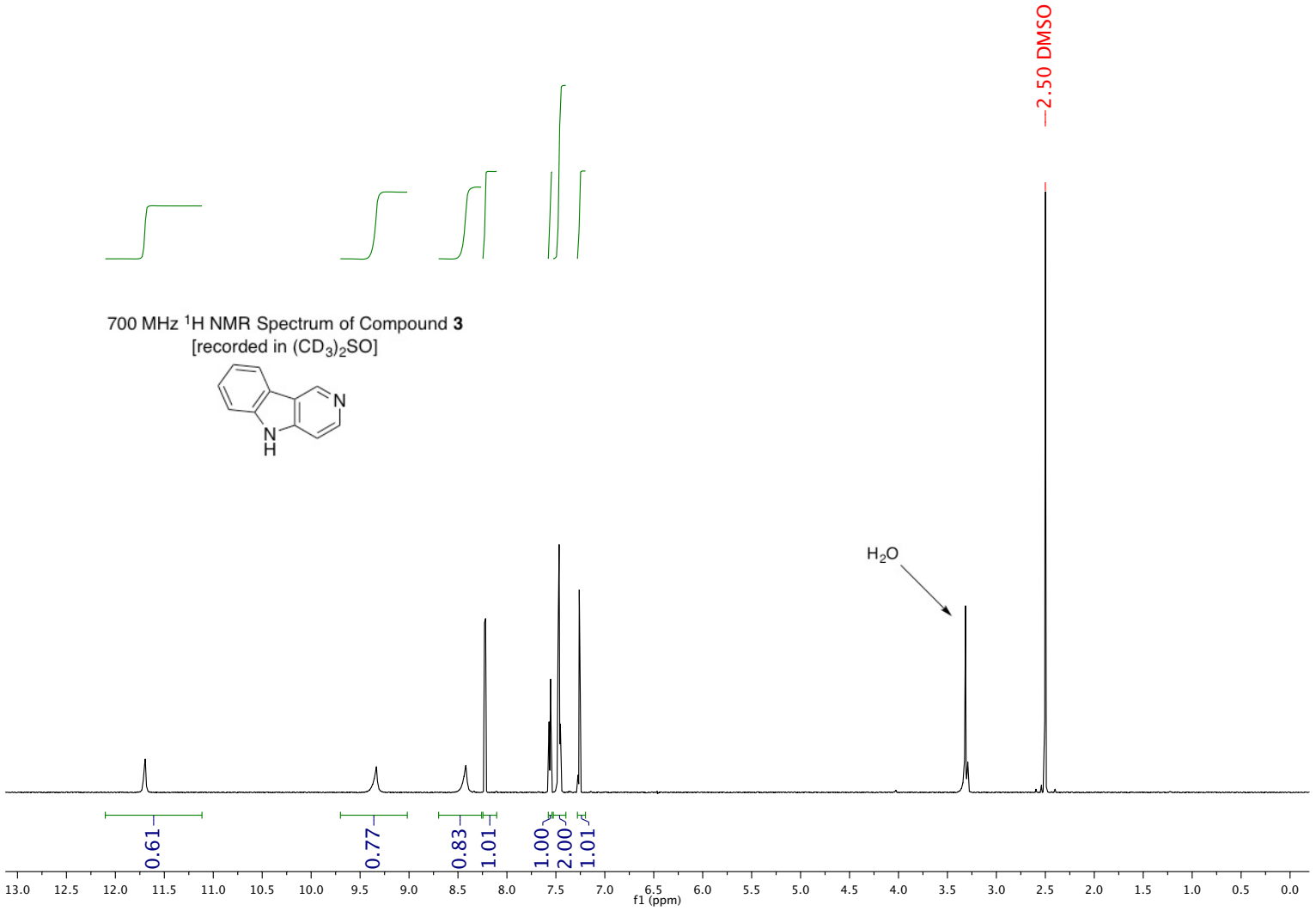

152.90
146.13
140.57
129.94
128.03
122.04
121.88
121.02
118.04
116.10
112.30
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
100 MHz 13C NMR Spectrum of Compound 1
(recorded in CD3OD)
N
H
N
122.04
121.88
122.2
122.0
121.8
f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

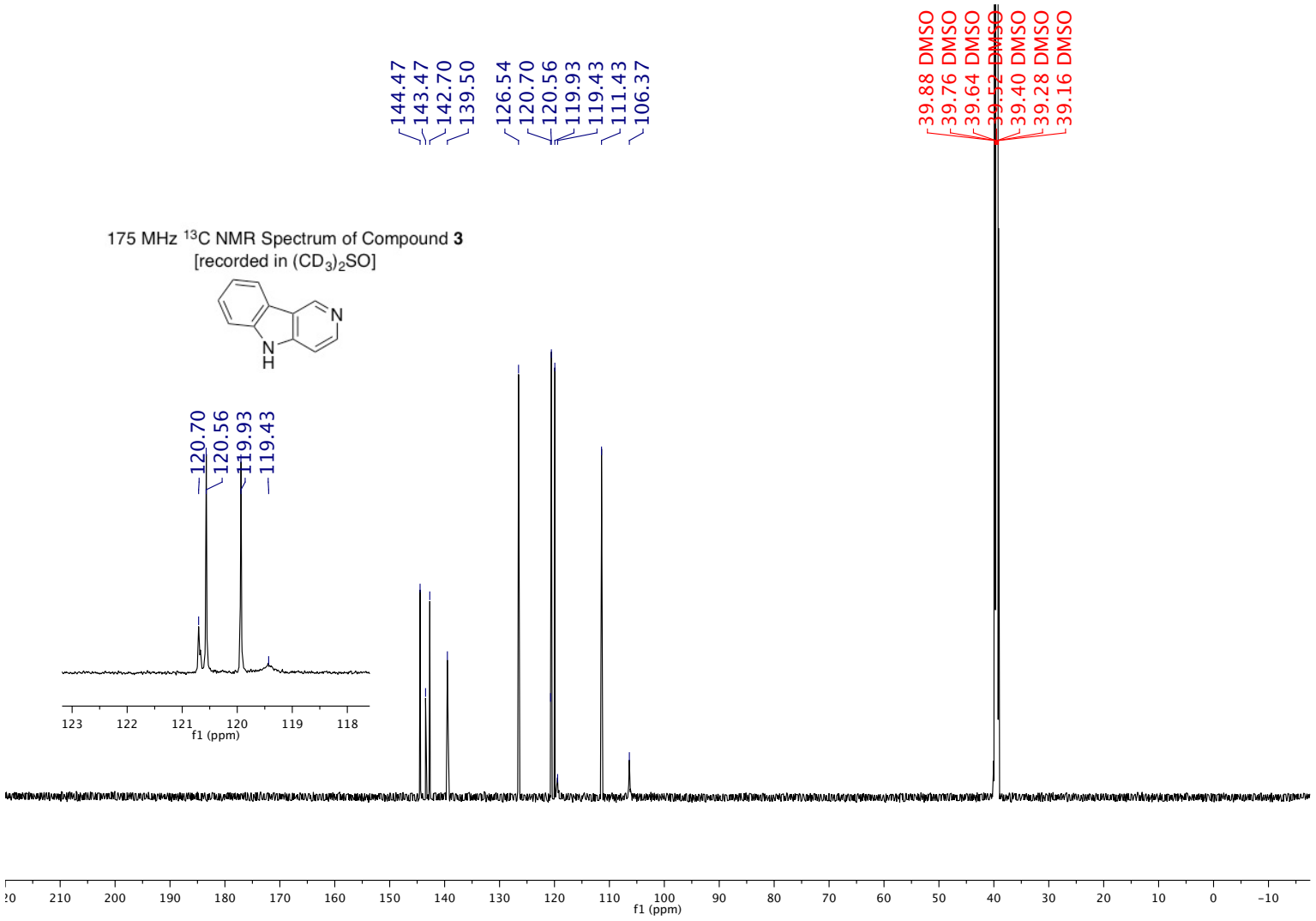

400 MHz ¹H NMR Spectrum of Compound 2
(recorded in CD3OD)
H2O
3.31 MeOD
1.00
1.00
1.00
1.00
2.00
1.00
f1 (ppm)

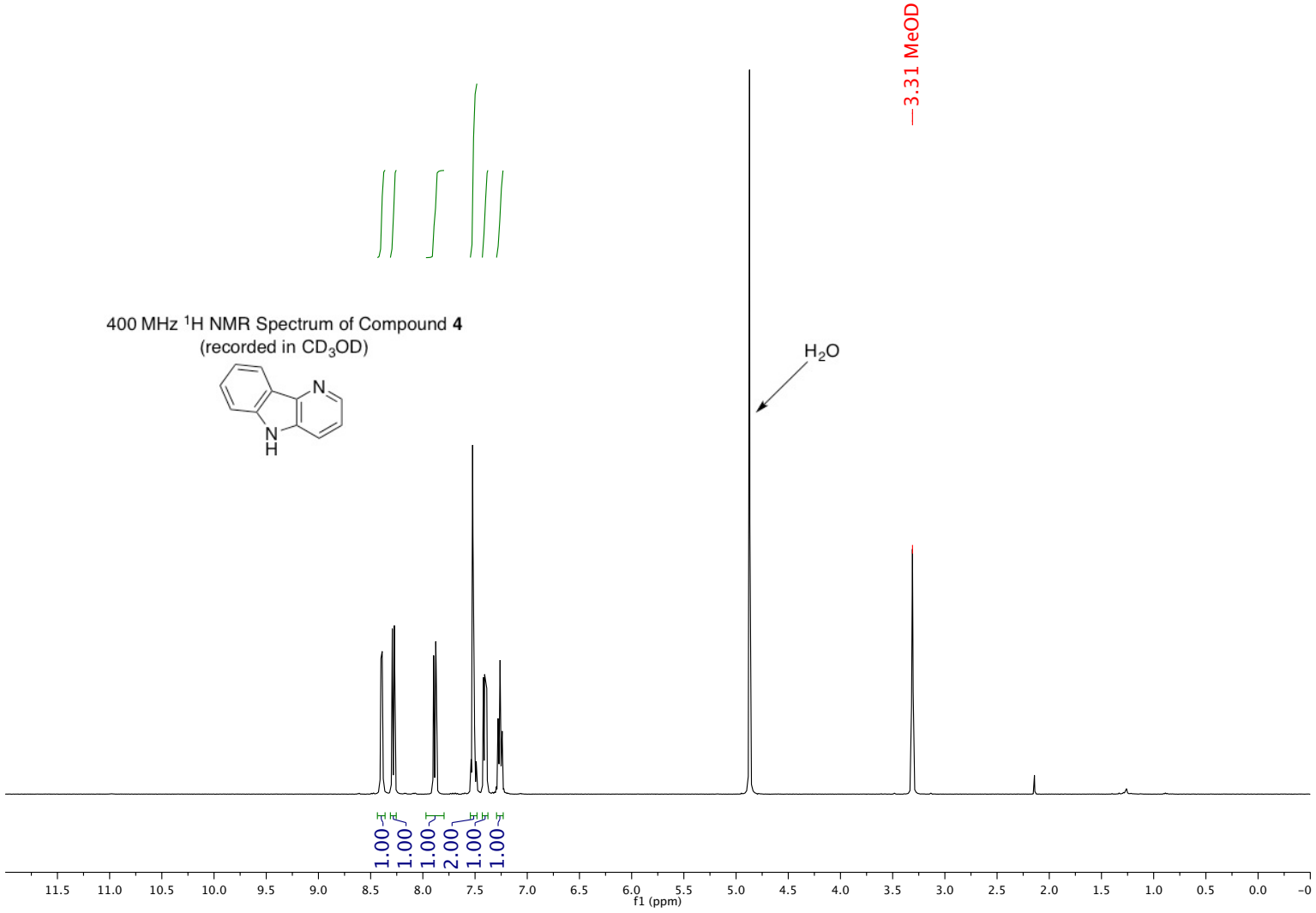

142.74
138.36
137.76
134.06
130.43
129.74
122.71
122.18
120.83
116.07
112.82
49.64 MeOD
49.42 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
100 MHz ^{13}C NMR Spectrum of Compound **2**
(recorded in CD_3OD)
N
H
N
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

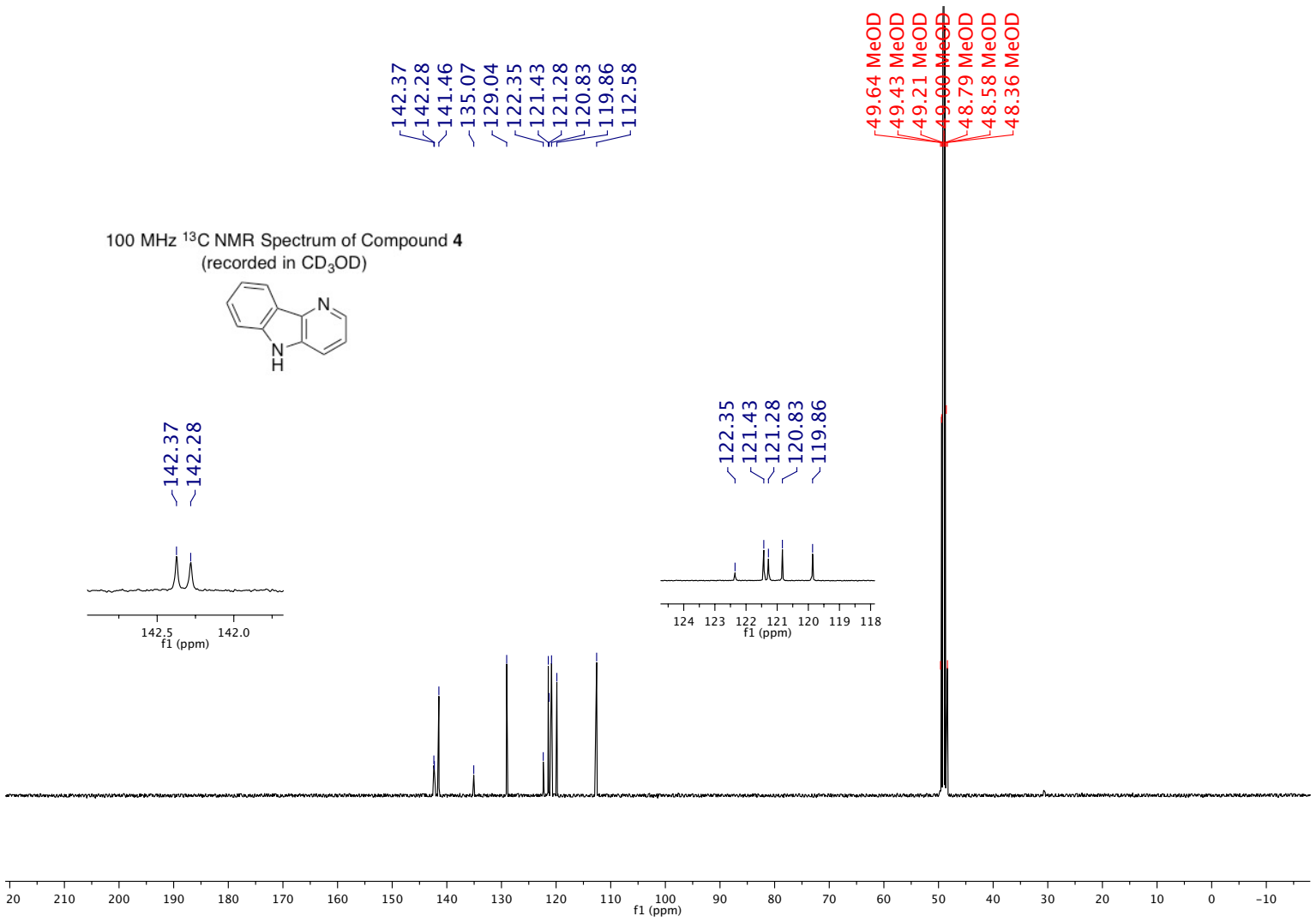

700 MHz ¹H NMR Spectrum of Compound 3
(recorded in CD3OD)
N
N
H
3.31 MeOD
H2O
acetone
1.00
1.00
1.00
1.00
2.00
1.00
f1 (ppm)

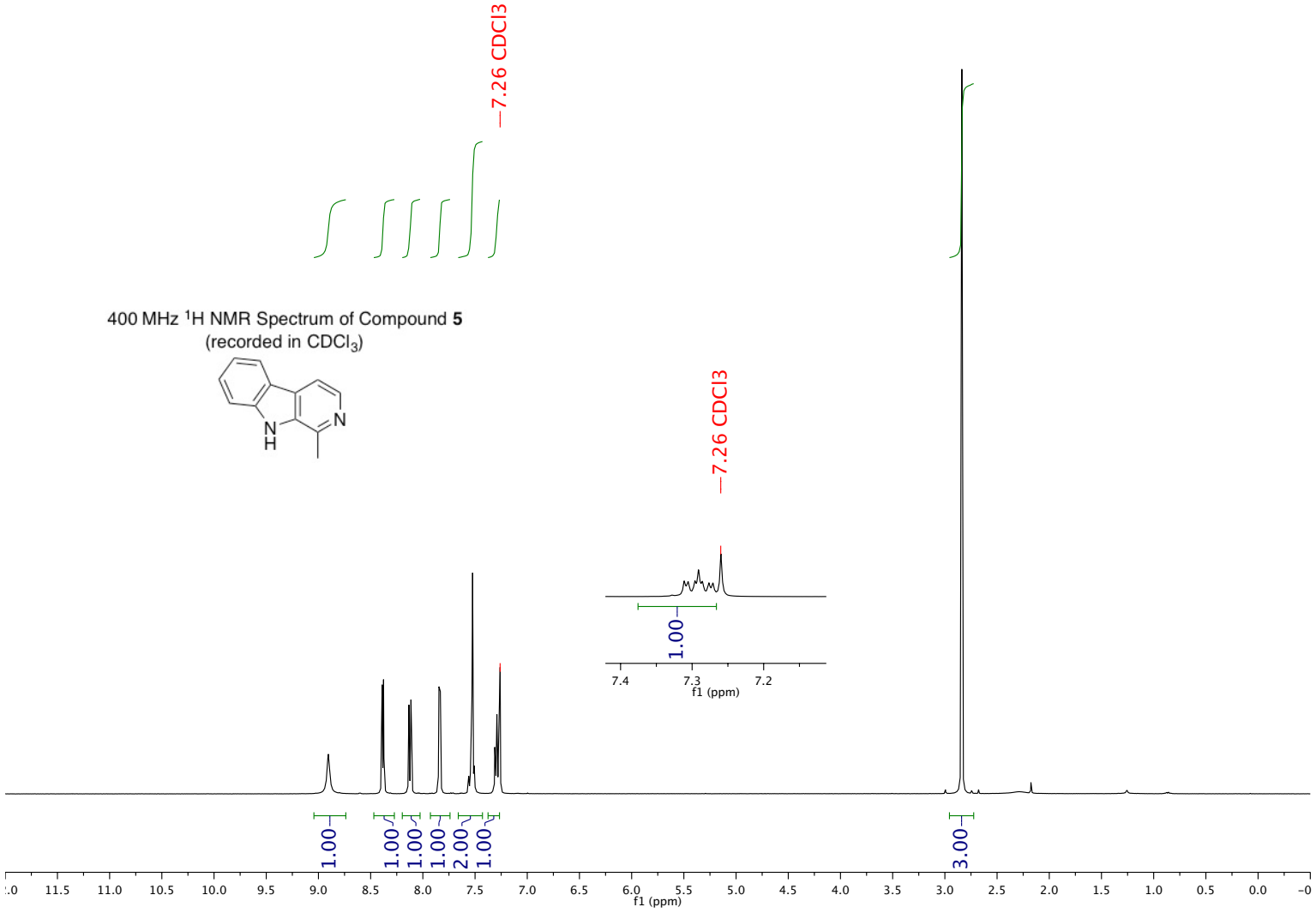

145.82
144.40
142.71
141.50
128.17
122.42
121.64
121.60
121.53
112.42
107.62
49.36 MeOD
49.24 MeOD
49.12 MeOD
49.00 MeOD
48.88 MeOD
48.76 MeOD
48.64 MeOD
175 MHz ^{13}C NMR Spectrum of Compound **3**
(recorded in CD_3OD)
N
N
H
122.42
121.64
121.60
121.53
123
122
121
120
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

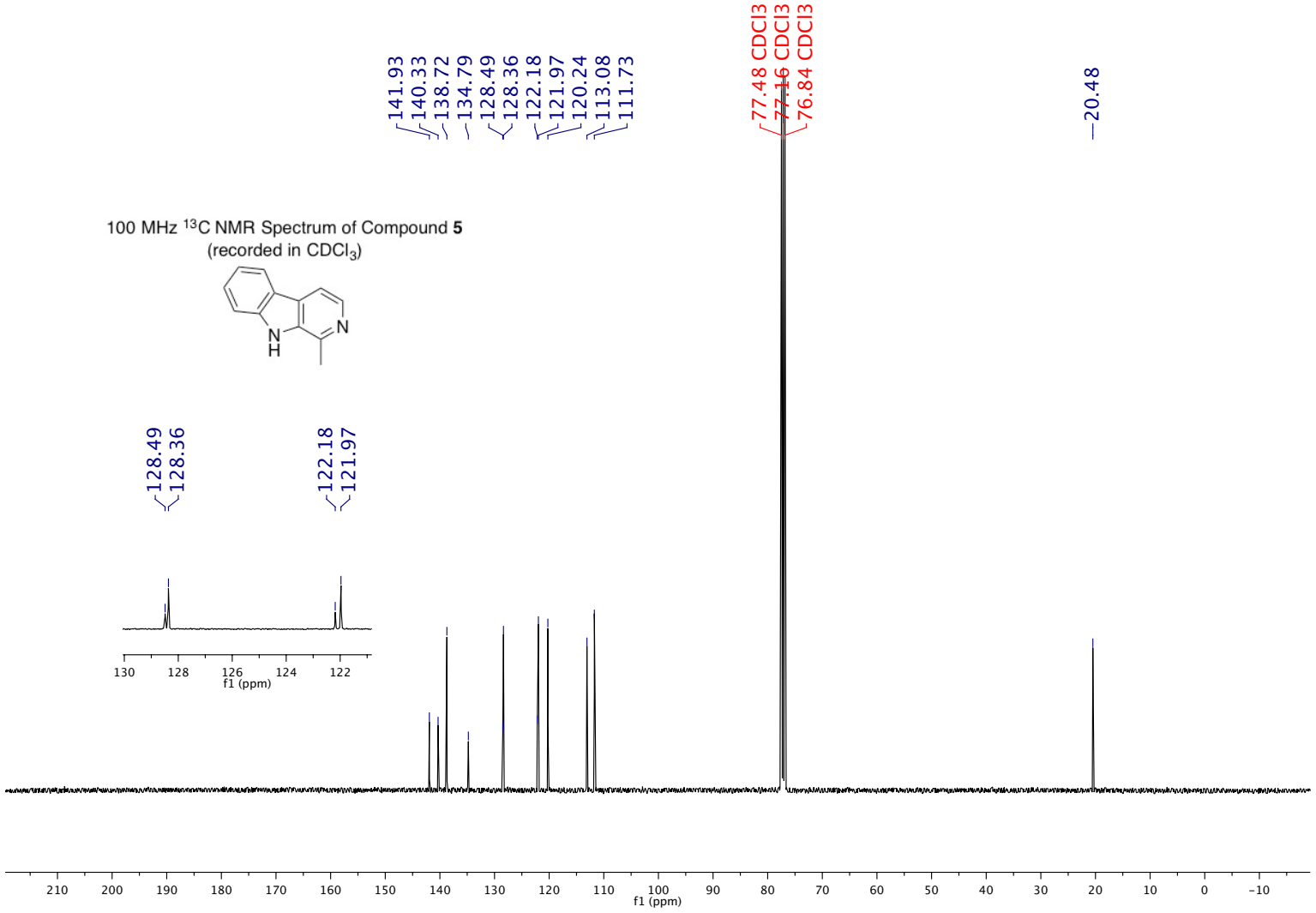

700 MHz ^{1}H NMR Spectrum of Compound **3**
[recorded in $(CD_3)_2SO$]
N
N
H
2.50 DMSO
H_2O
0.61
0.77
0.83
1.01
1.00
2.00
1.01
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

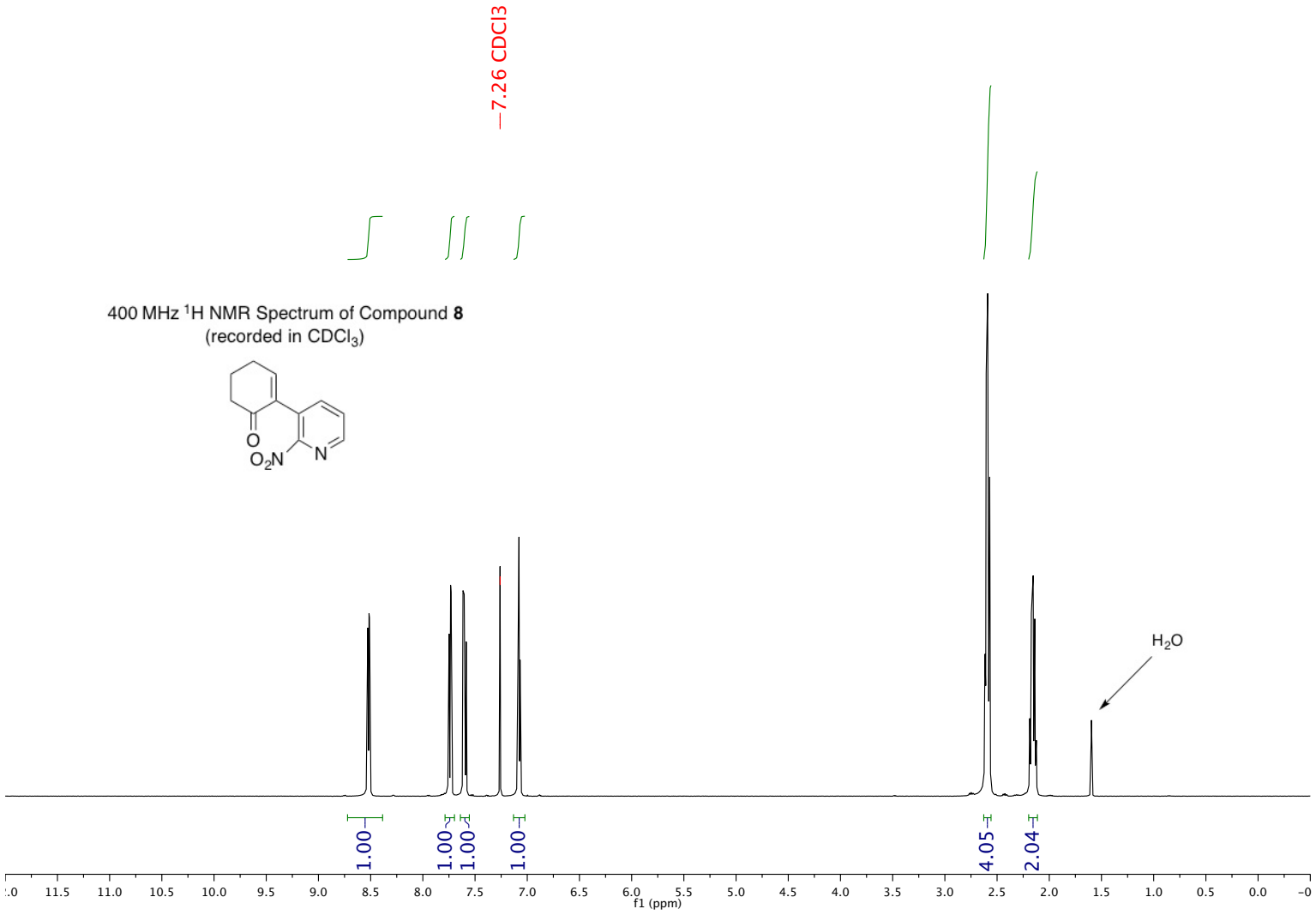

144.47
143.47
142.70
139.50
126.54
120.70
120.56
119.93
119.43
111.43
106.37
39.88 DMSO
39.76 DMSO
39.64 DMSO
39.52 DMSO
39.40 DMSO
39.28 DMSO
39.16 DMSO
175 MHz 13C NMR Spectrum of Compound 3
[recorded in (CD3)2SO]
N
N
H
120.70
120.56
119.93
119.43
123
122
121
120
119
118
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

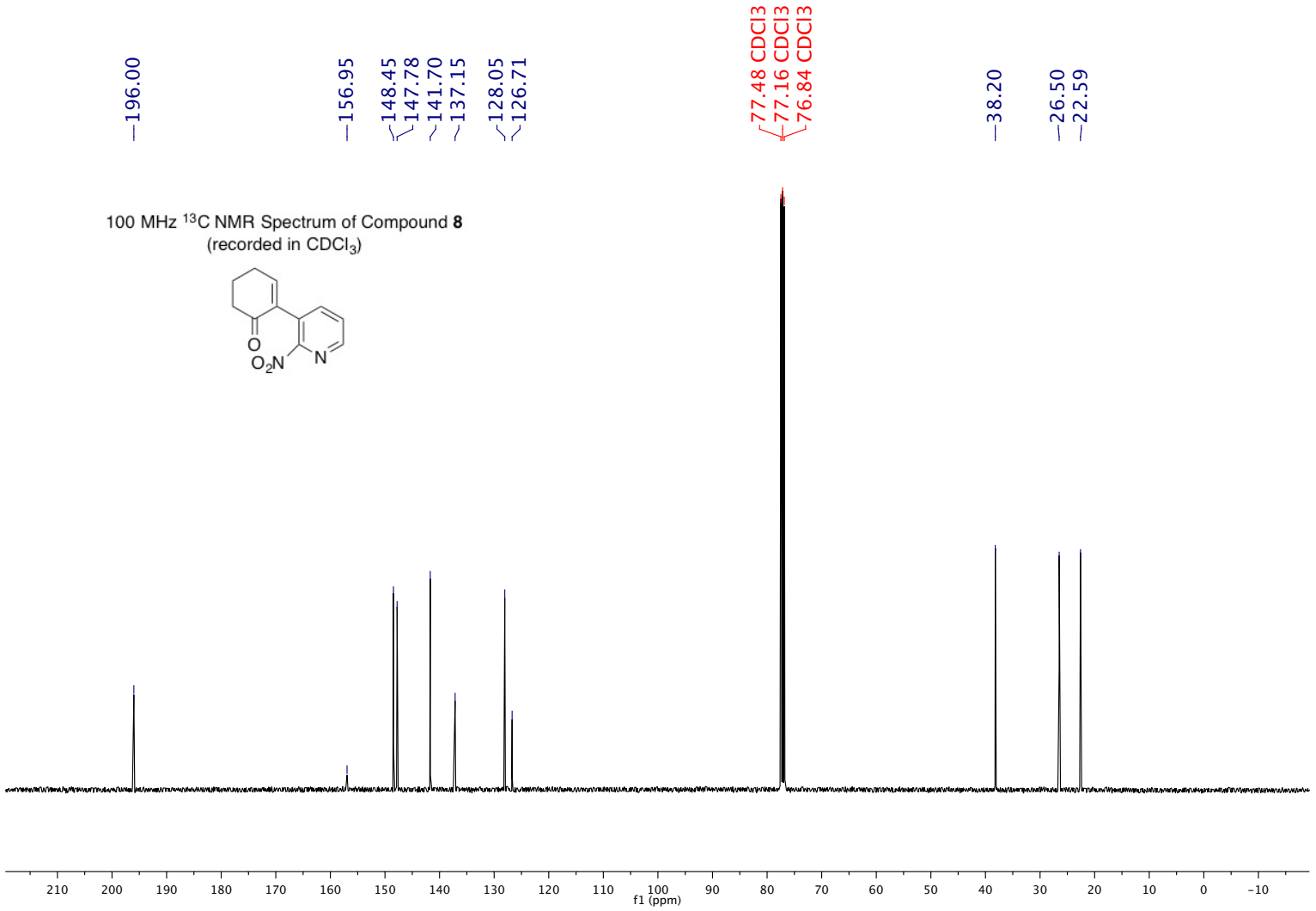

400 MHz ¹H NMR Spectrum of Compound 4
(recorded in CD3OD)
N
N
H
3.31 MeOD
H2O
1.00
1.00
1.00
2.00
1.00
1.00
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

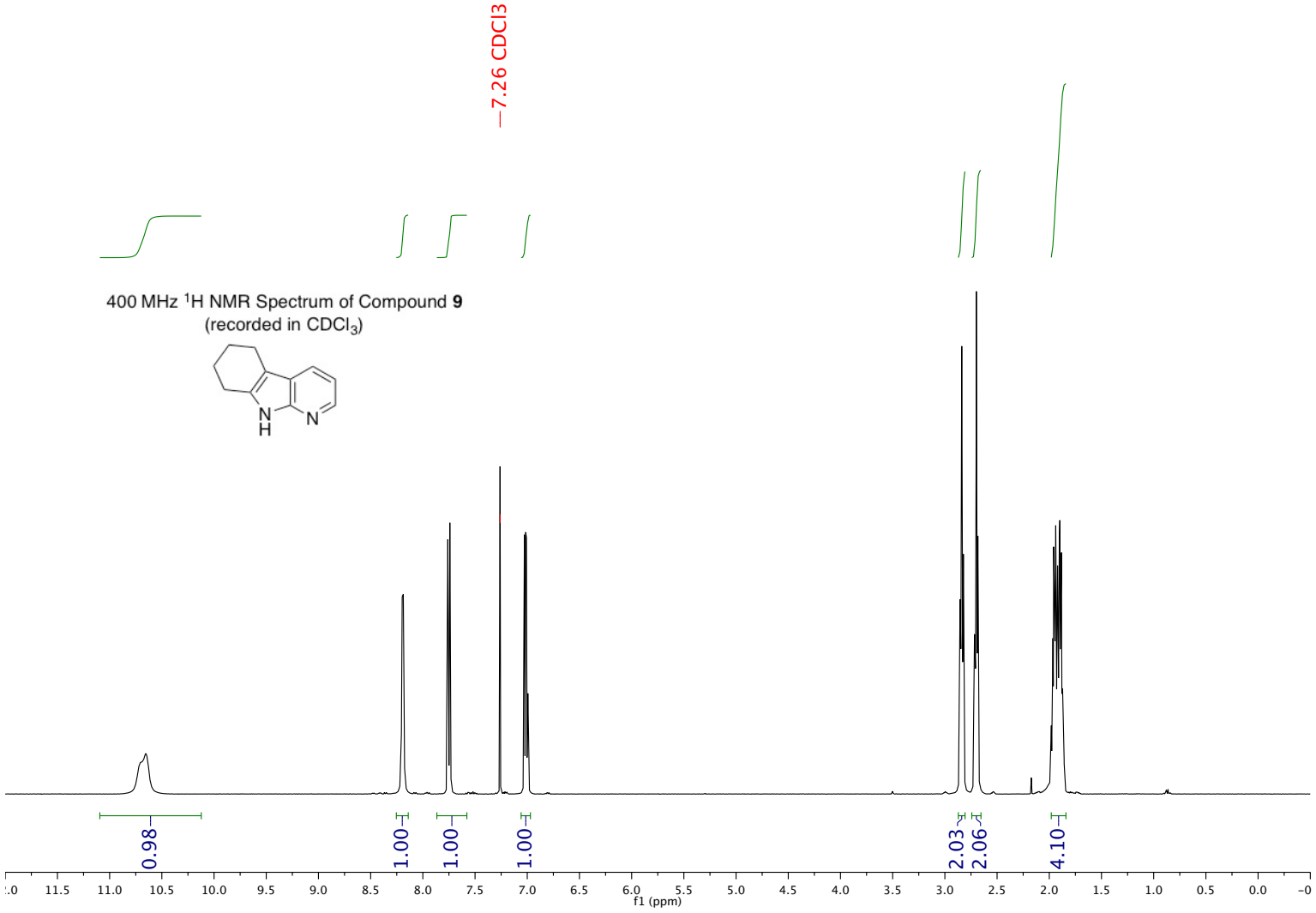

100 MHz ^{13}C NMR Spectrum of Compound **4**
(recorded in CD_3OD)
142.37
142.28
141.46
135.07
129.04
122.35
121.43
121.28
120.83
119.86
112.58
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.58 MeOD
48.36 MeOD
142.37
142.28
142.5
142.0
f1 (ppm)
122.35
121.43
121.28
120.83
119.86
124 123 122 121 120 119 118
f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

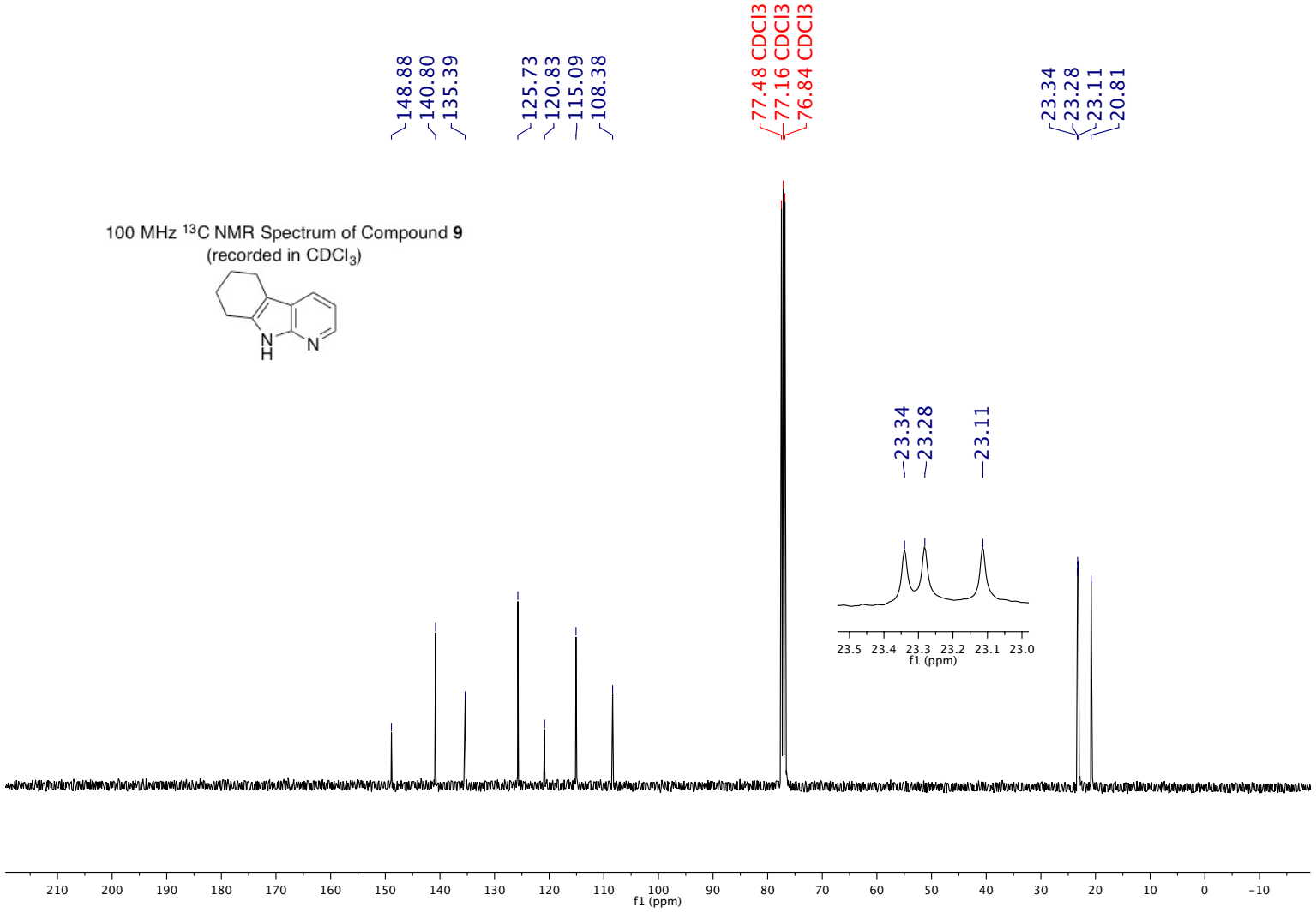

400 MHz ¹H NMR Spectrum of Compound 5
(recorded in CDCl3)
7.26 CDCl3
7.26 CDCl3
1.00
1.00
1.00
1.00
2.00
1.00
3.00
f1 (ppm)
f1 (ppm)

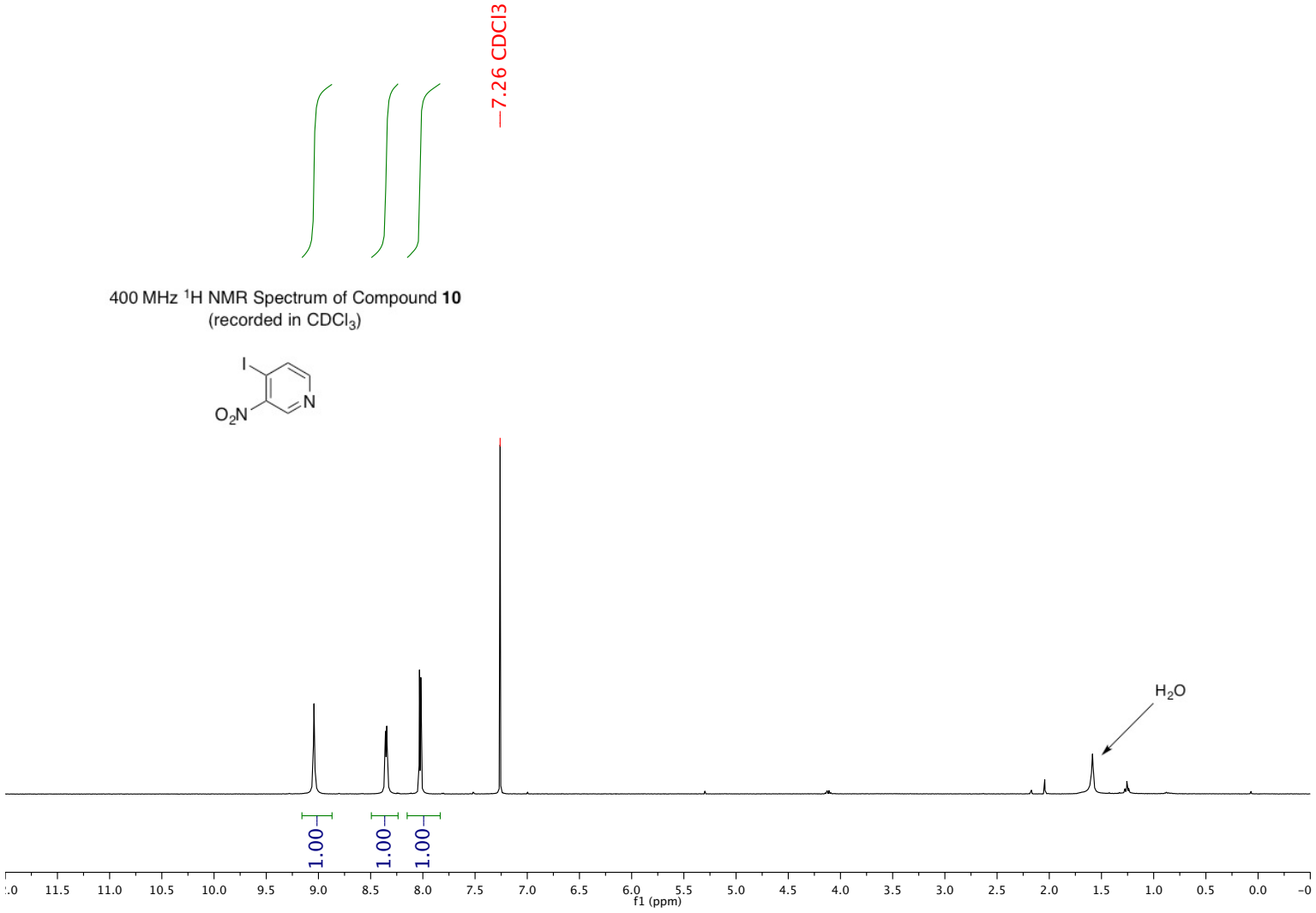

100 MHz ^{13}C NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)
141.93
140.33
138.72
134.79
128.49
128.36
122.18
121.97
120.24
113.08
111.73
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
20.48
N
H
N
128.49
128.36
122.18
121.97
130
128
126
124
122
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

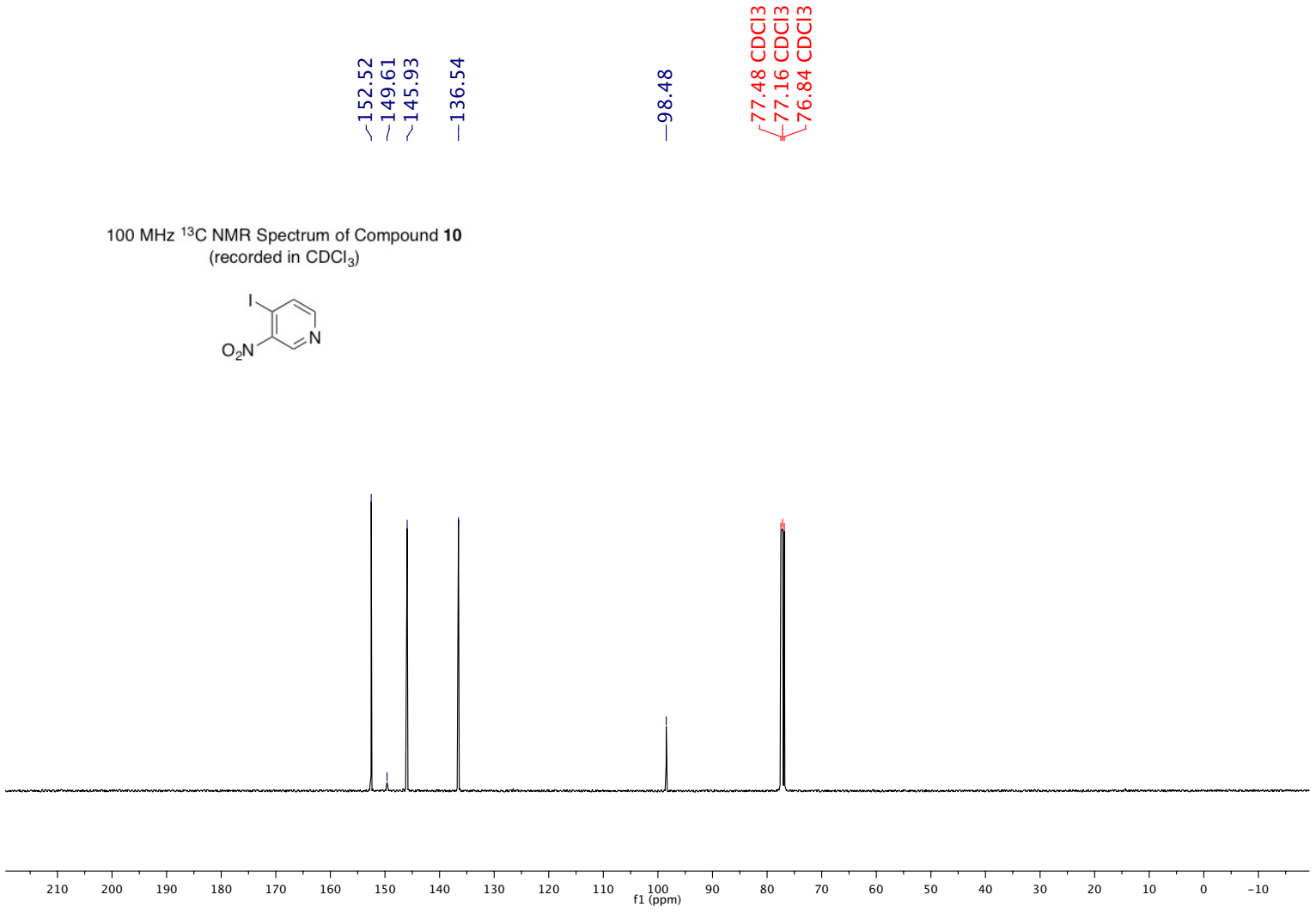

7.26 CDCl3
400 MHz ¹H NMR Spectrum of Compound 8
(recorded in CDCl3)
O
O2N
N
H2O
1.00
1.00
1.00
1.00
4.05
2.04
f1 (ppm)


196.00
156.95
148.45
147.78
141.70
137.15
128.05
126.71
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.20
26.50
22.59
100 MHz 13C NMR Spectrum of Compound 8
(recorded in CDCl3)
O
O2N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

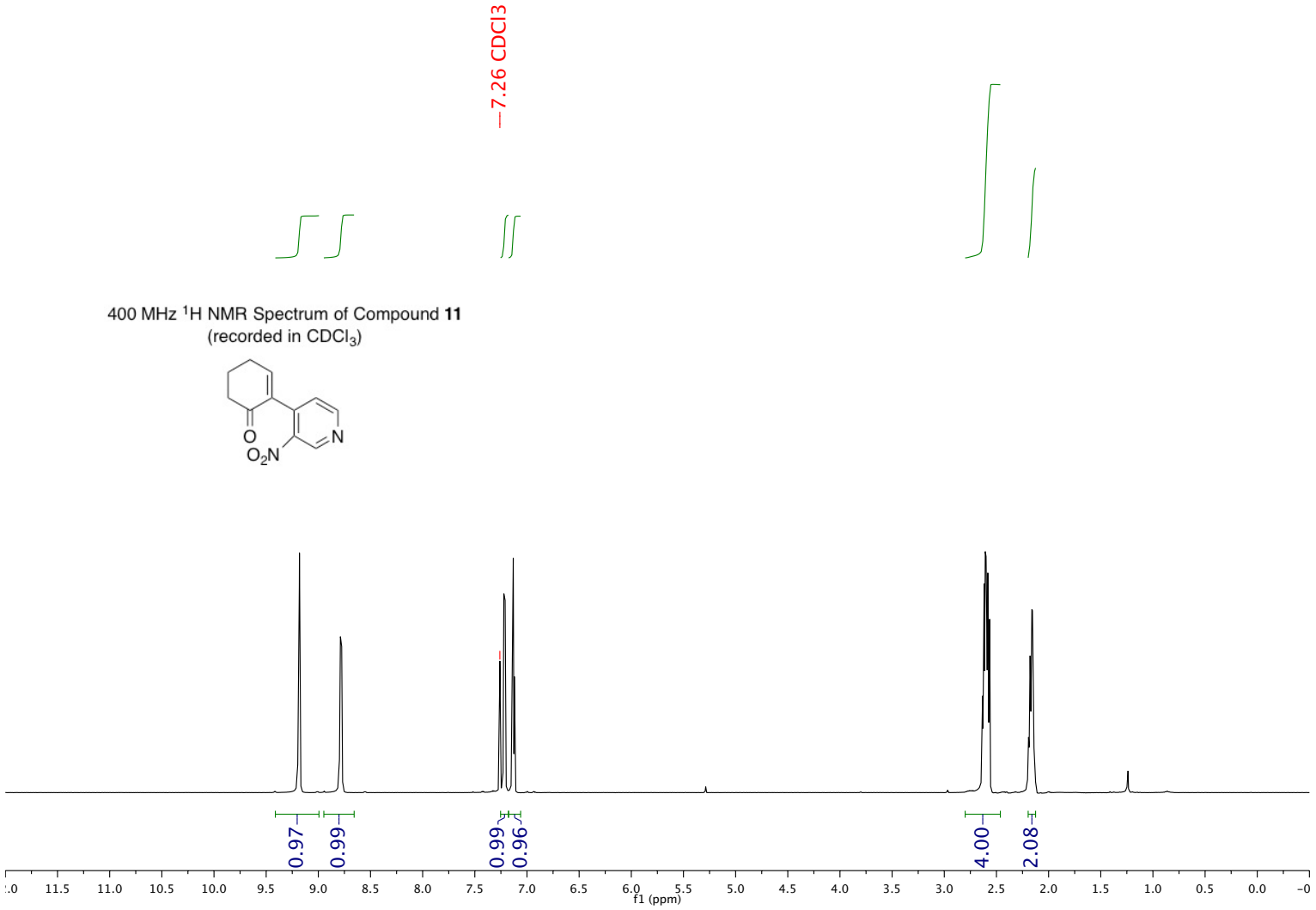

400 MHz ¹H NMR Spectrum of Compound 9
(recorded in CDCl3)
7.26 CDCl3
0.98
1.00
1.00
1.00
2.03
2.06
4.10
f1 (ppm)


148.88
140.80
135.39
125.73
120.83
115.09
108.38
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
23.34
23.28
23.11
20.81
100 MHz 13C NMR Spectrum of Compound 9
(recorded in CDCl3)
N
H
N
23.34
23.28
23.11
23.5 23.4 23.3 23.2 23.1 23.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

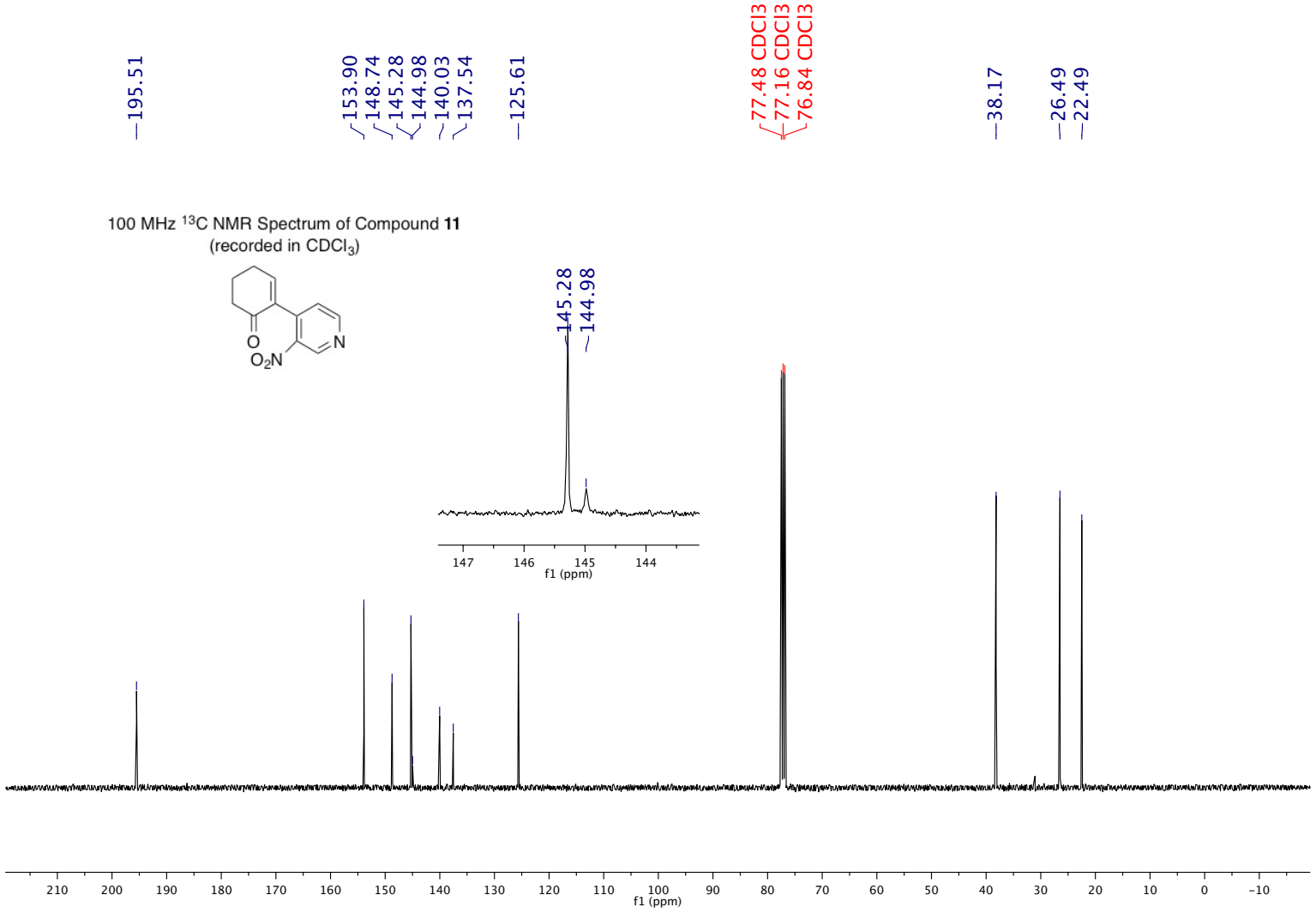

7.26 CDCl3
400 MHz ¹H NMR Spectrum of Compound 10
(recorded in CDCl3)
I
O2N
N
H2O
1.00
1.00
1.00
f1 (ppm)

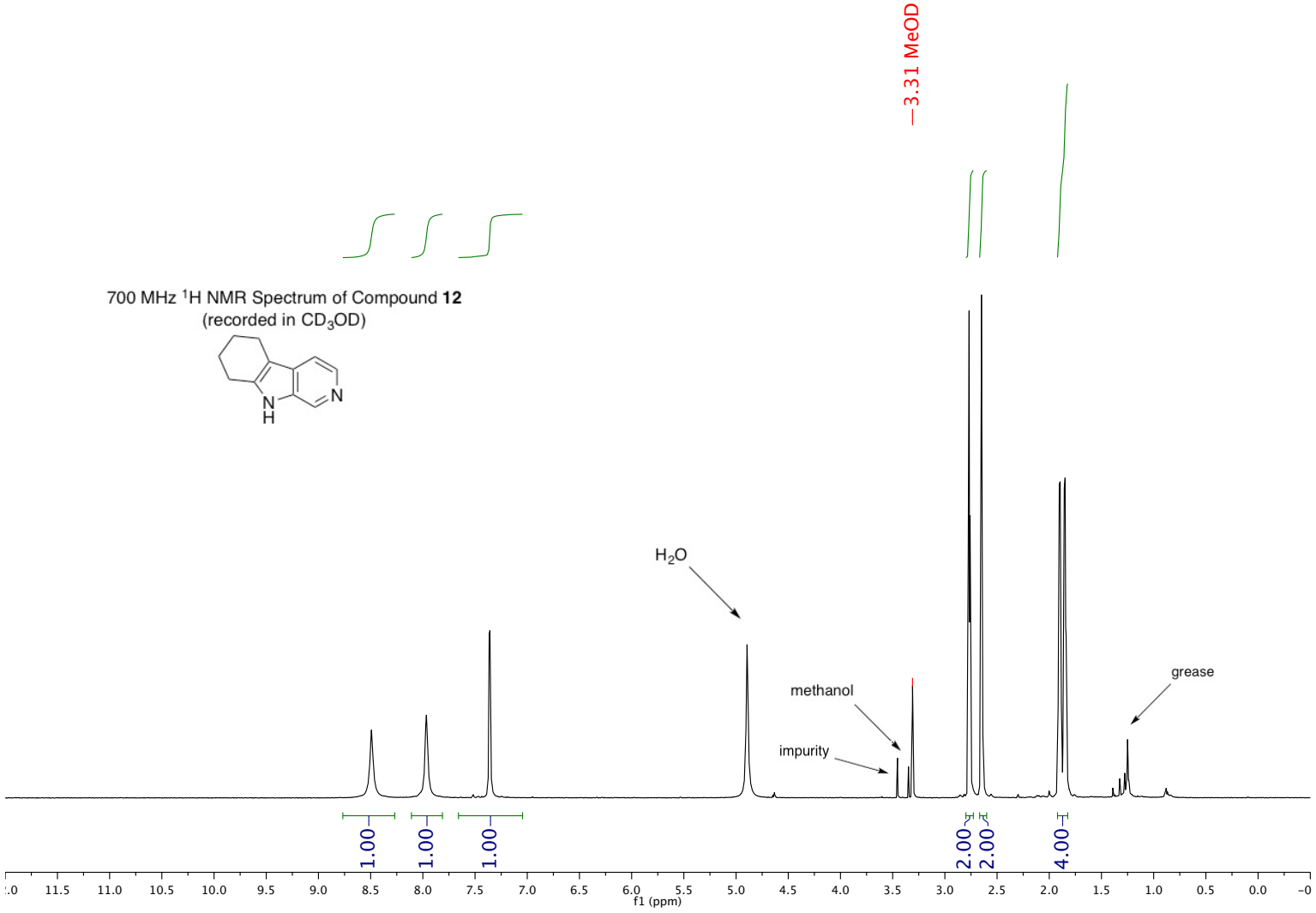


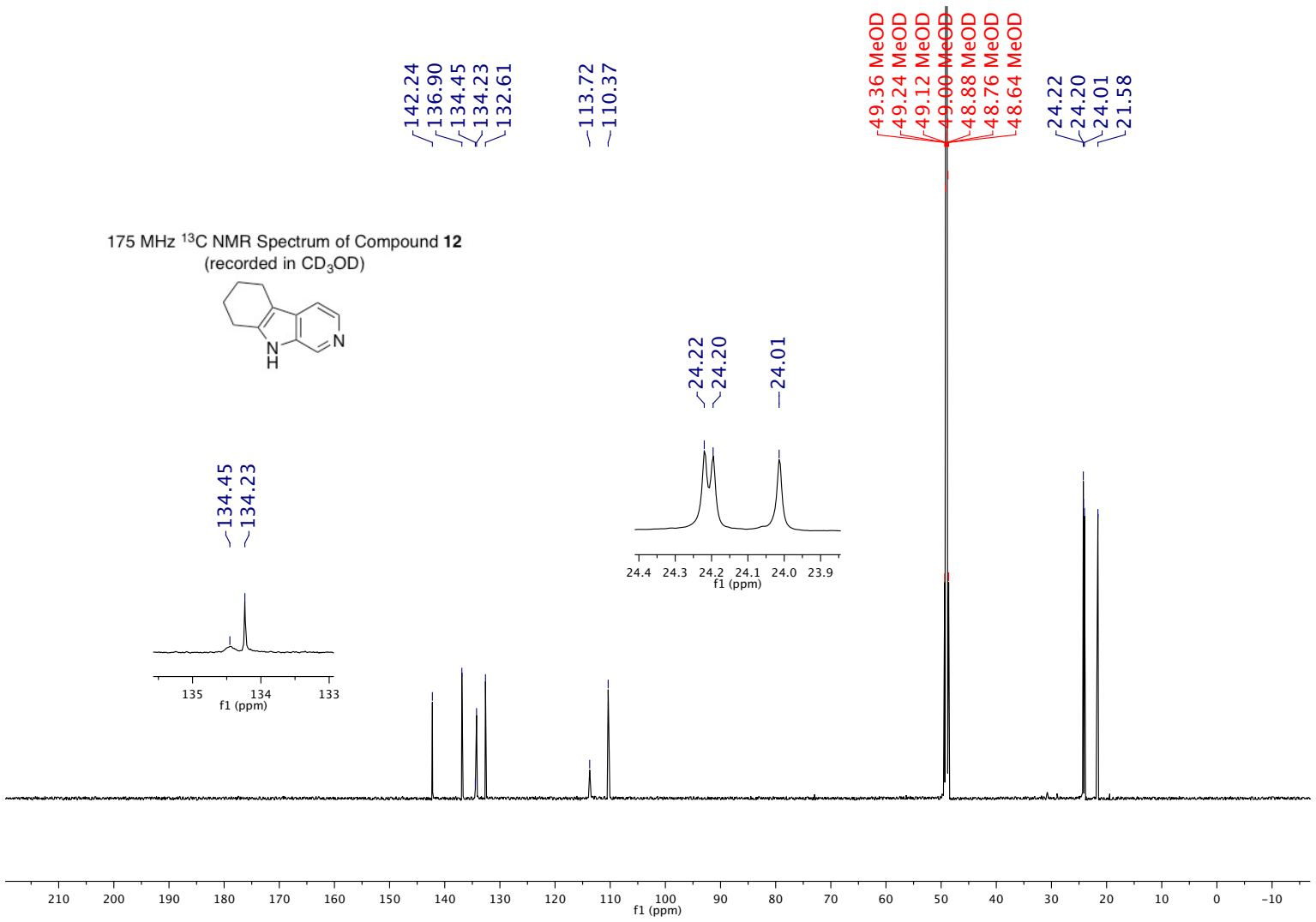
100 MHz ^{13}C NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

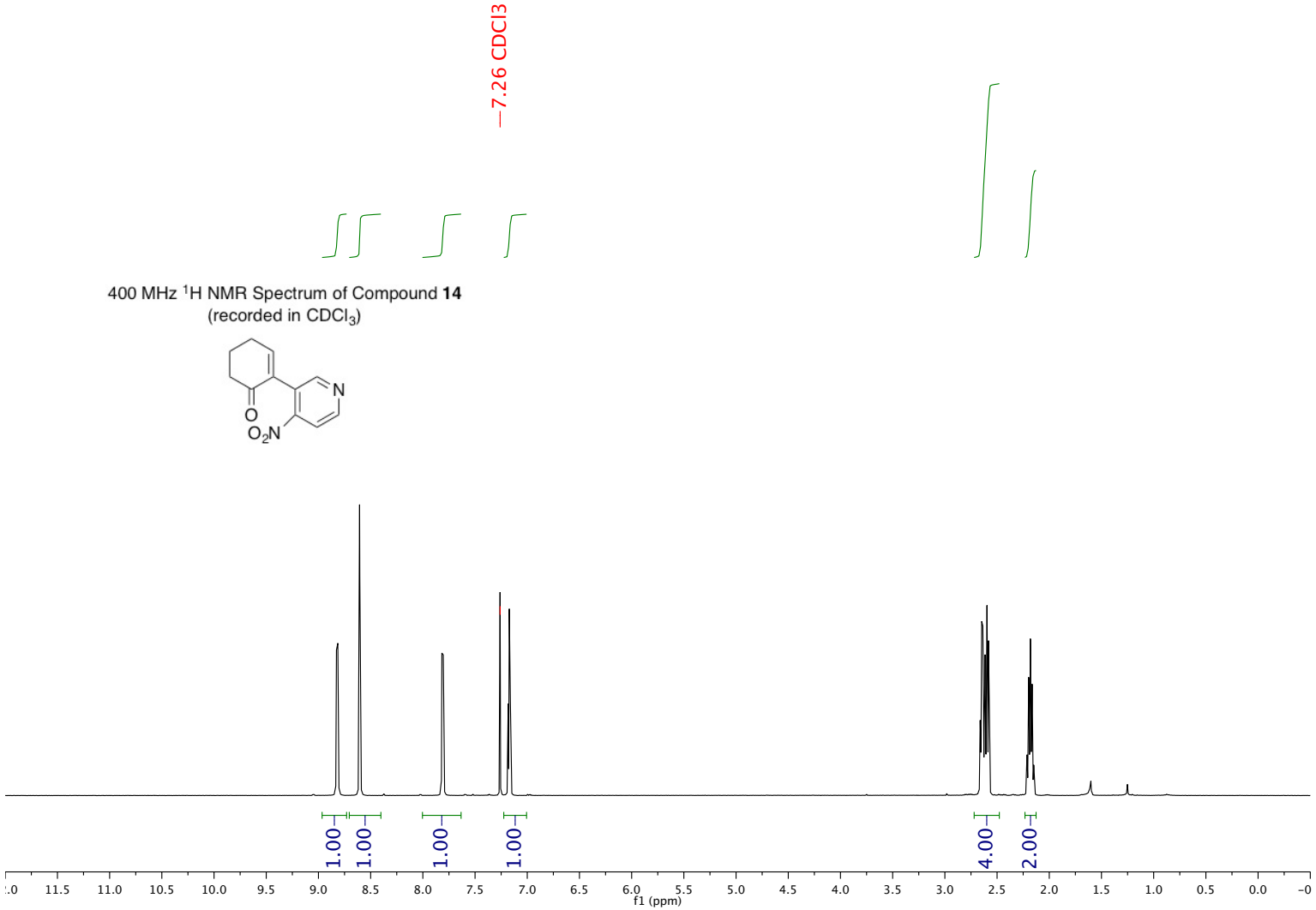


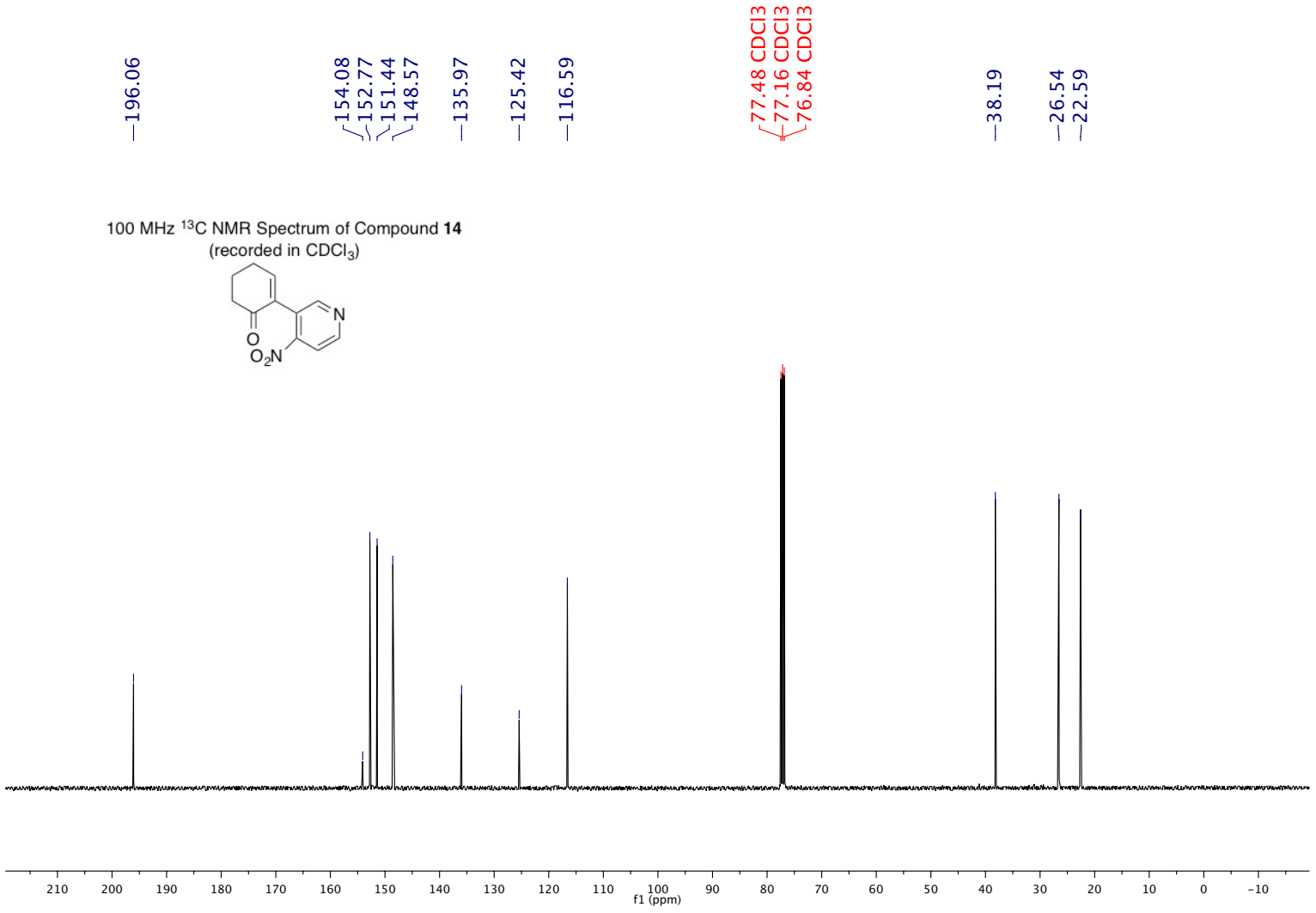
400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)

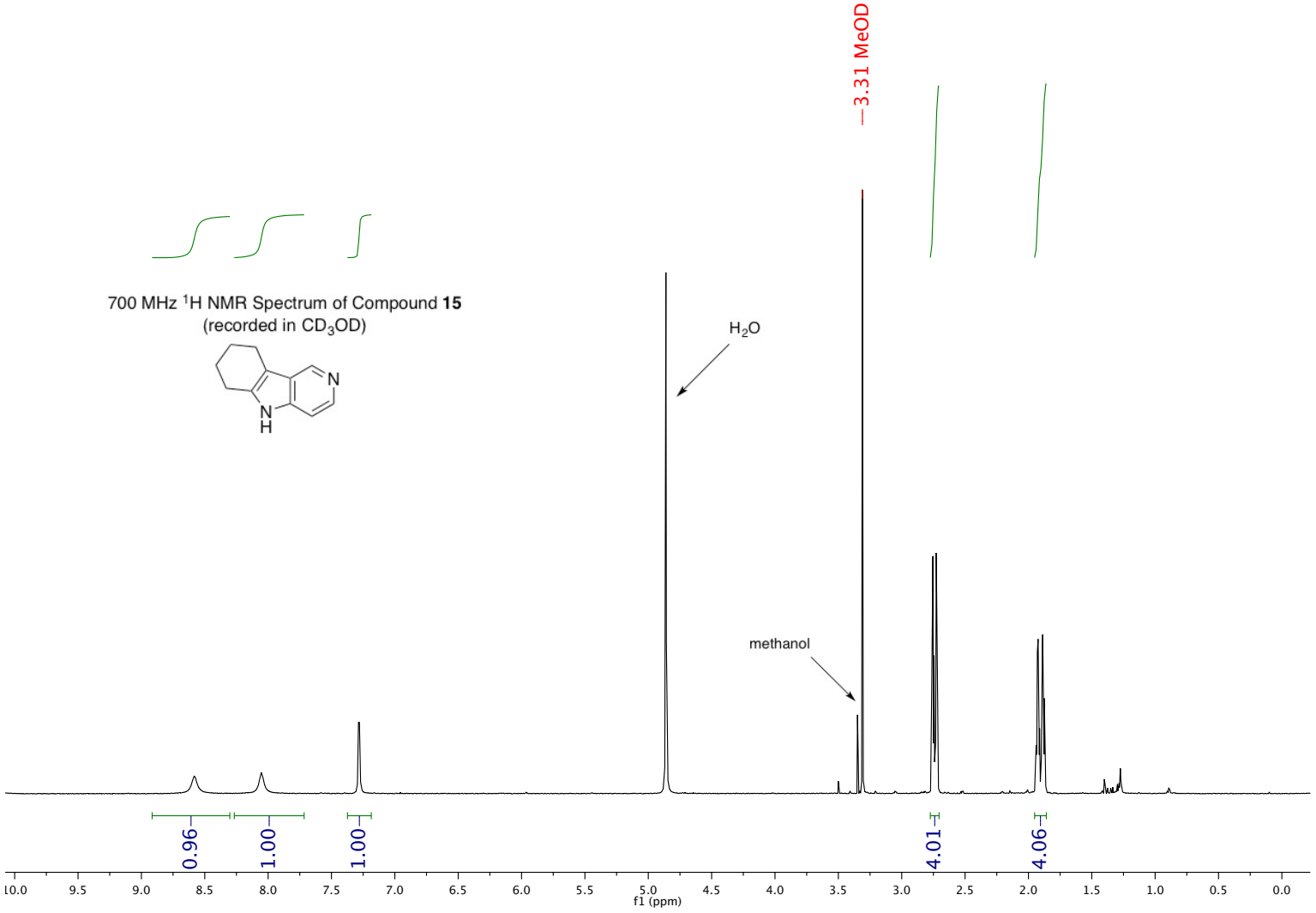

195.51
153.90
148.74
145.28
144.98
140.03
137.54
125.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.17
26.49
22.49
100 MHz 13C NMR Spectrum of Compound 11
(recorded in CDCl3)
O
O2N
N
145.28
144.98
147
146
145
144
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

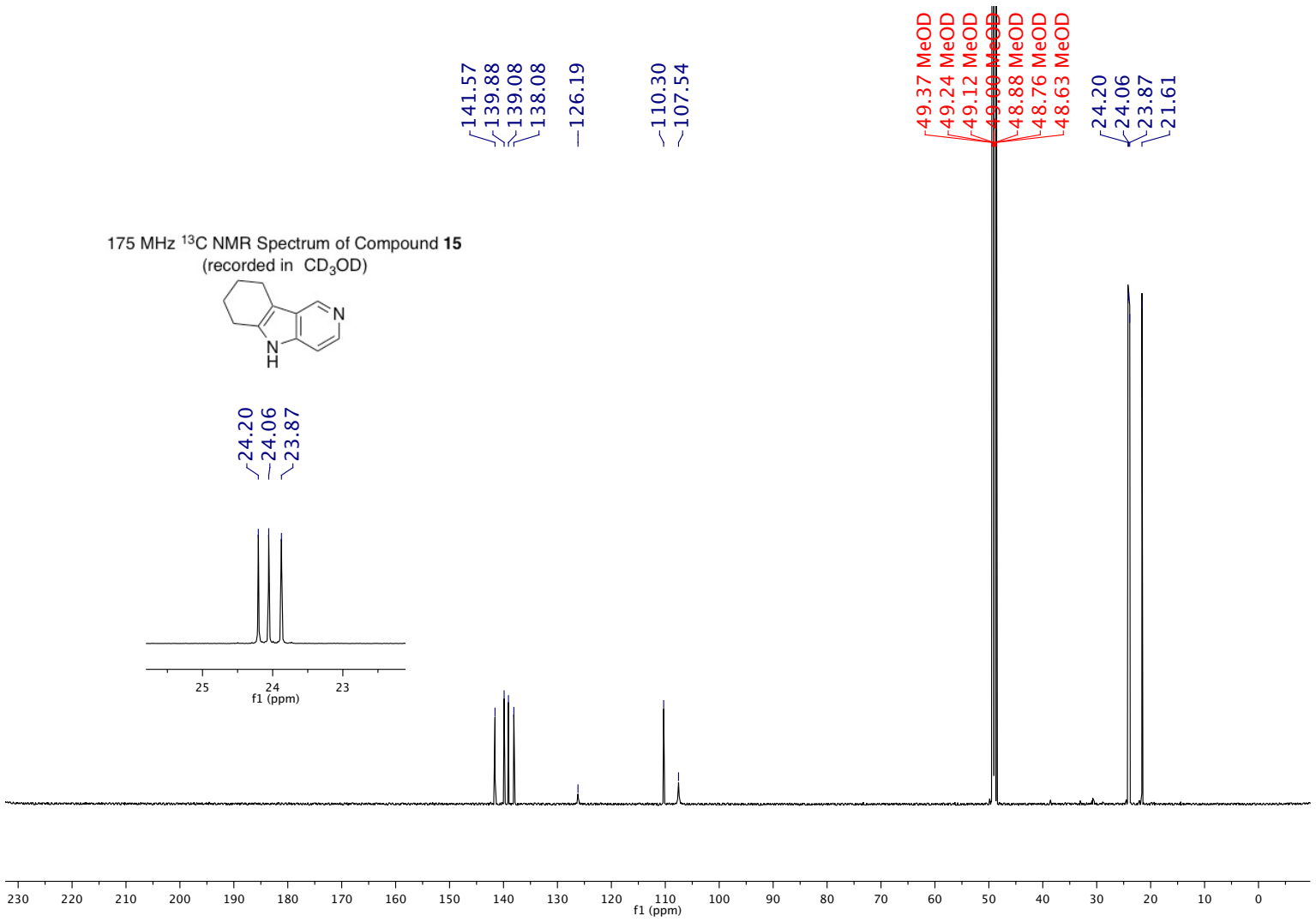

700 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in CD_3OD)
N
H
N
3.31 MeOD
H_2O
methanol
impurity
grease
1.00
1.00
1.00
2.00
2.00
4.00
f1 (ppm)

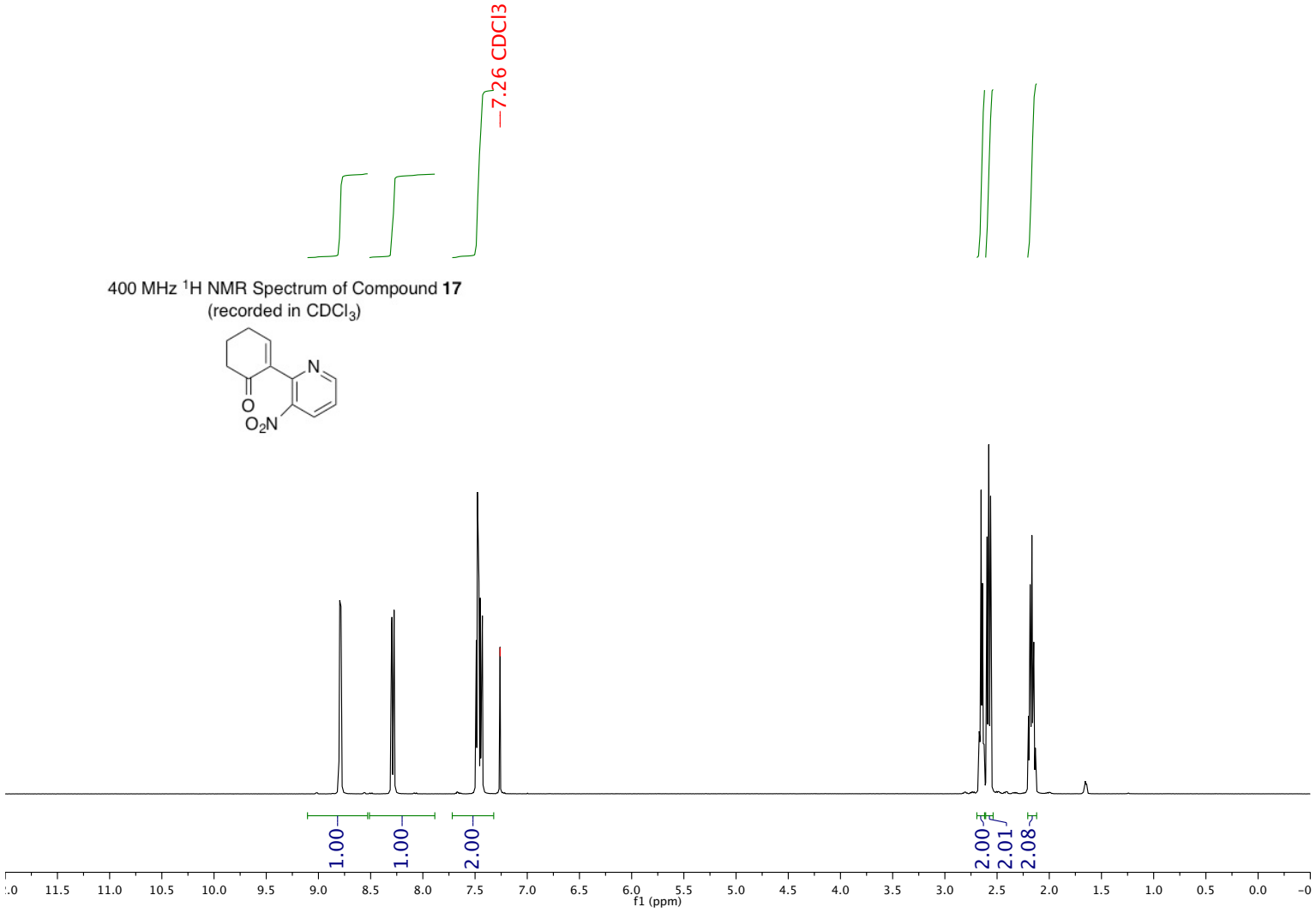

142.24
136.90
134.45
134.23
132.61
113.72
110.37
49.36 MeOD
49.24 MeOD
49.12 MeOD
49.00 MeOD
48.88 MeOD
48.76 MeOD
48.64 MeOD
24.22
24.20
24.01
21.58
175 MHz 13C NMR Spectrum of Compound 12
(recorded in CD3OD)
N
H
N
24.22
24.20
24.01
24.4 24.3 24.2 24.1 24.0 23.9
f1 (ppm)
134.45
134.23
135 134 133
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

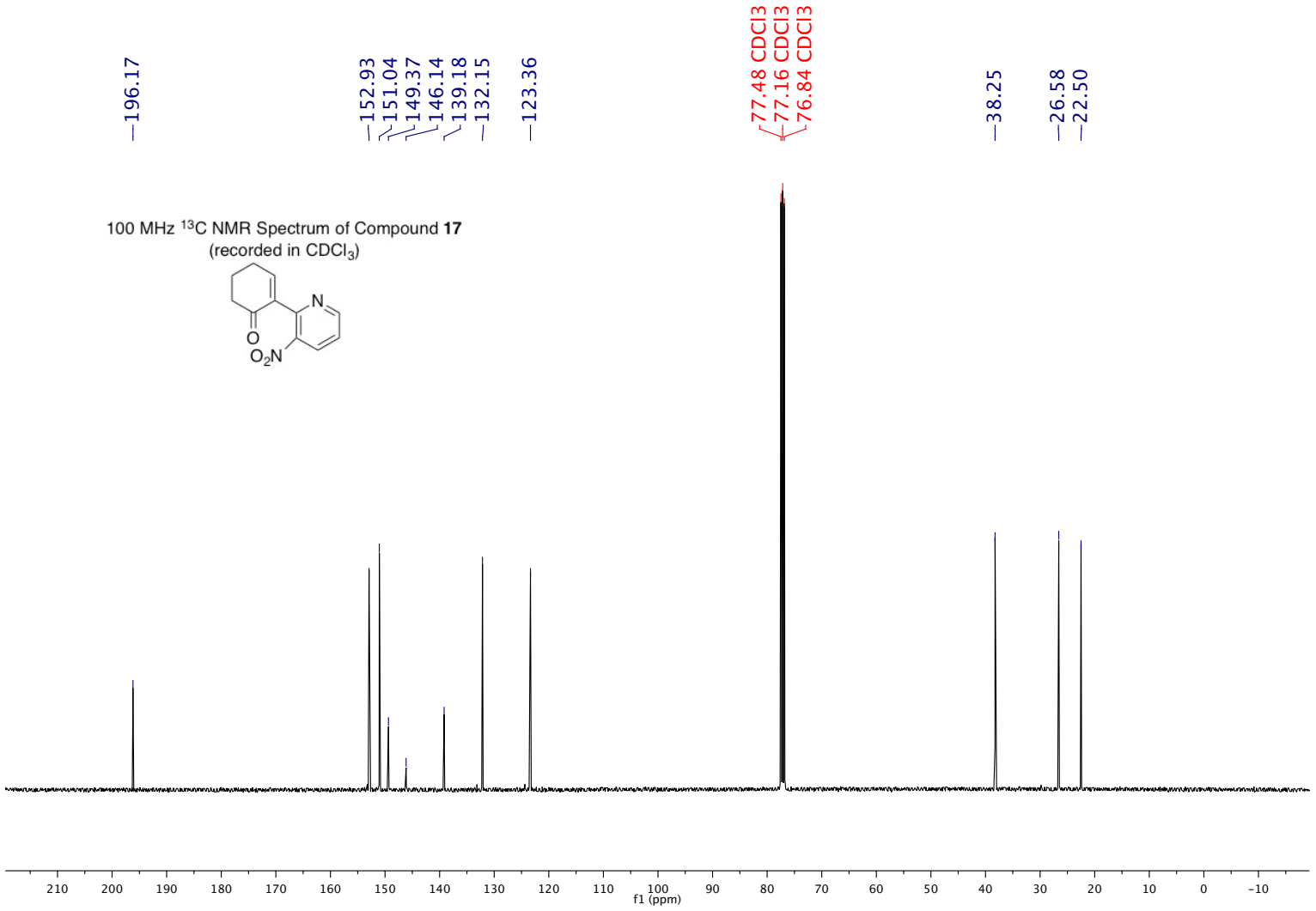

7.26 CDCl3
400 MHz ¹H NMR Spectrum of Compound 14
(recorded in CDCl3)
O
O2N
N
1.00
1.00
1.00
1.00
4.00
2.00
f1 (ppm)

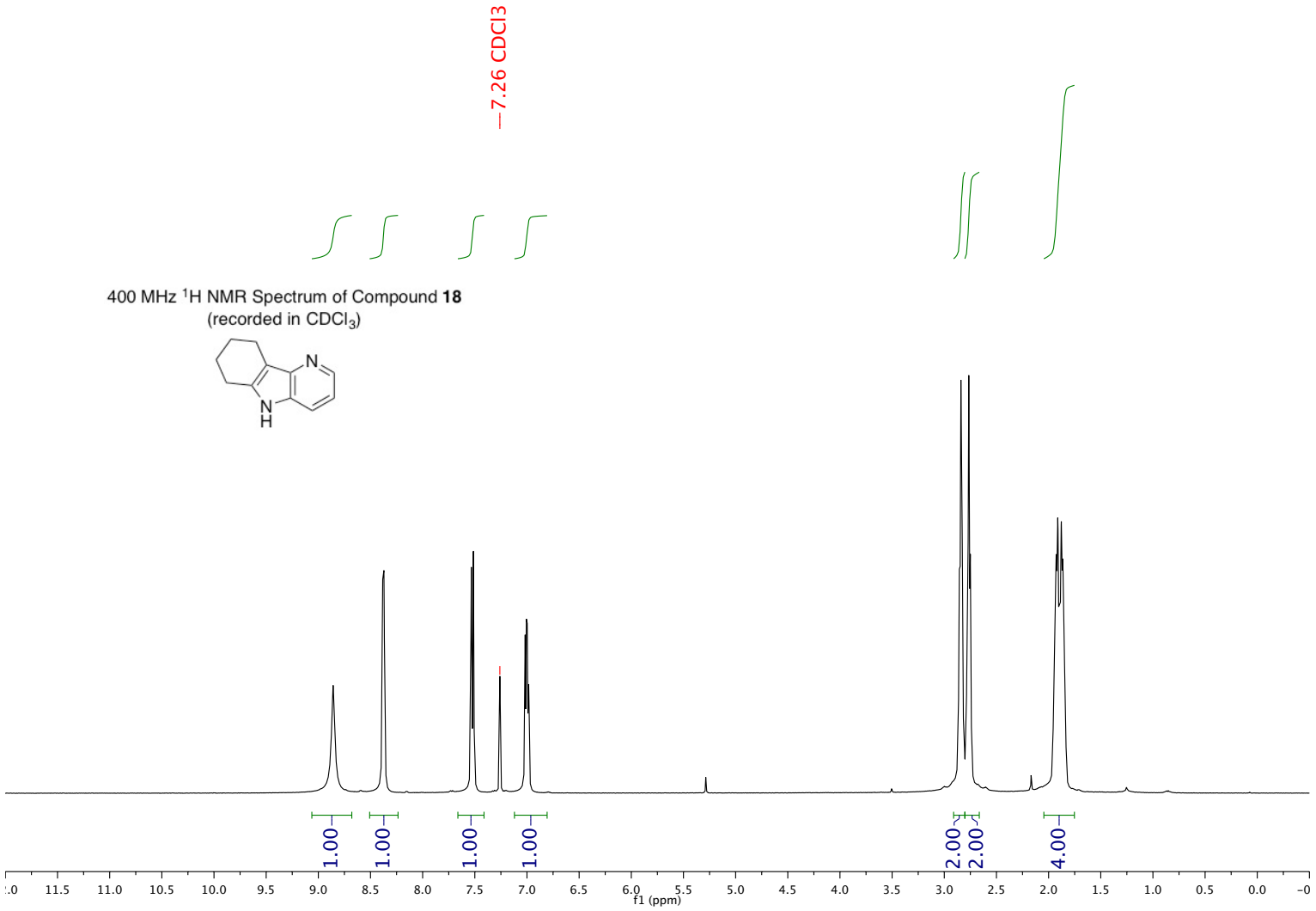

196.06
154.08
152.77
151.44
148.57
135.97
125.42
116.59
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.19
26.54
22.59
100 MHz 13C NMR Spectrum of Compound 14
(recorded in CDCl3)
O
O2N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

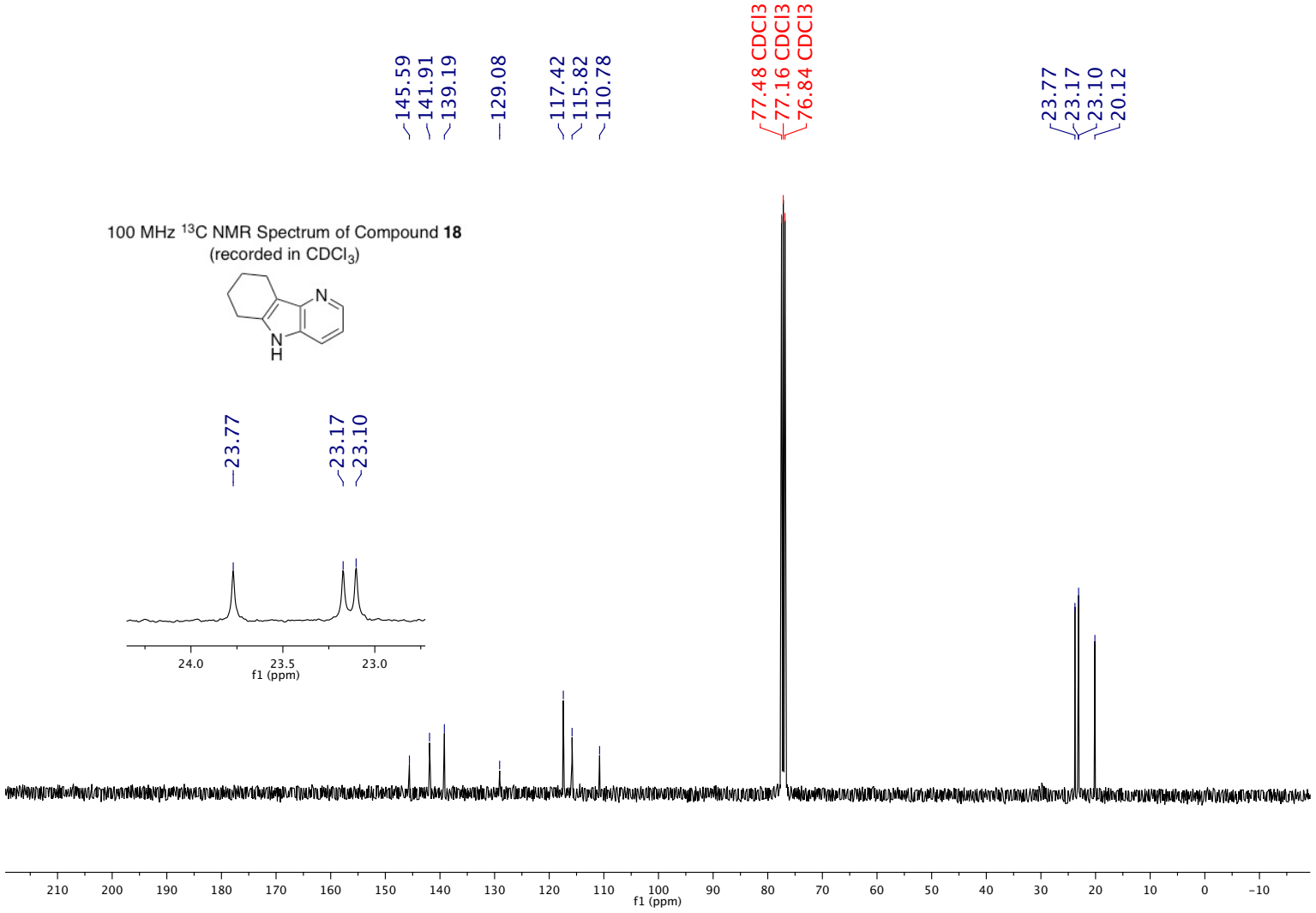

700 MHz ¹H NMR Spectrum of Compound 15
(recorded in CD3OD)
N
N
H
H2O
3.31 MeOD
methanol
0.96
1.00
1.00
4.01
4.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

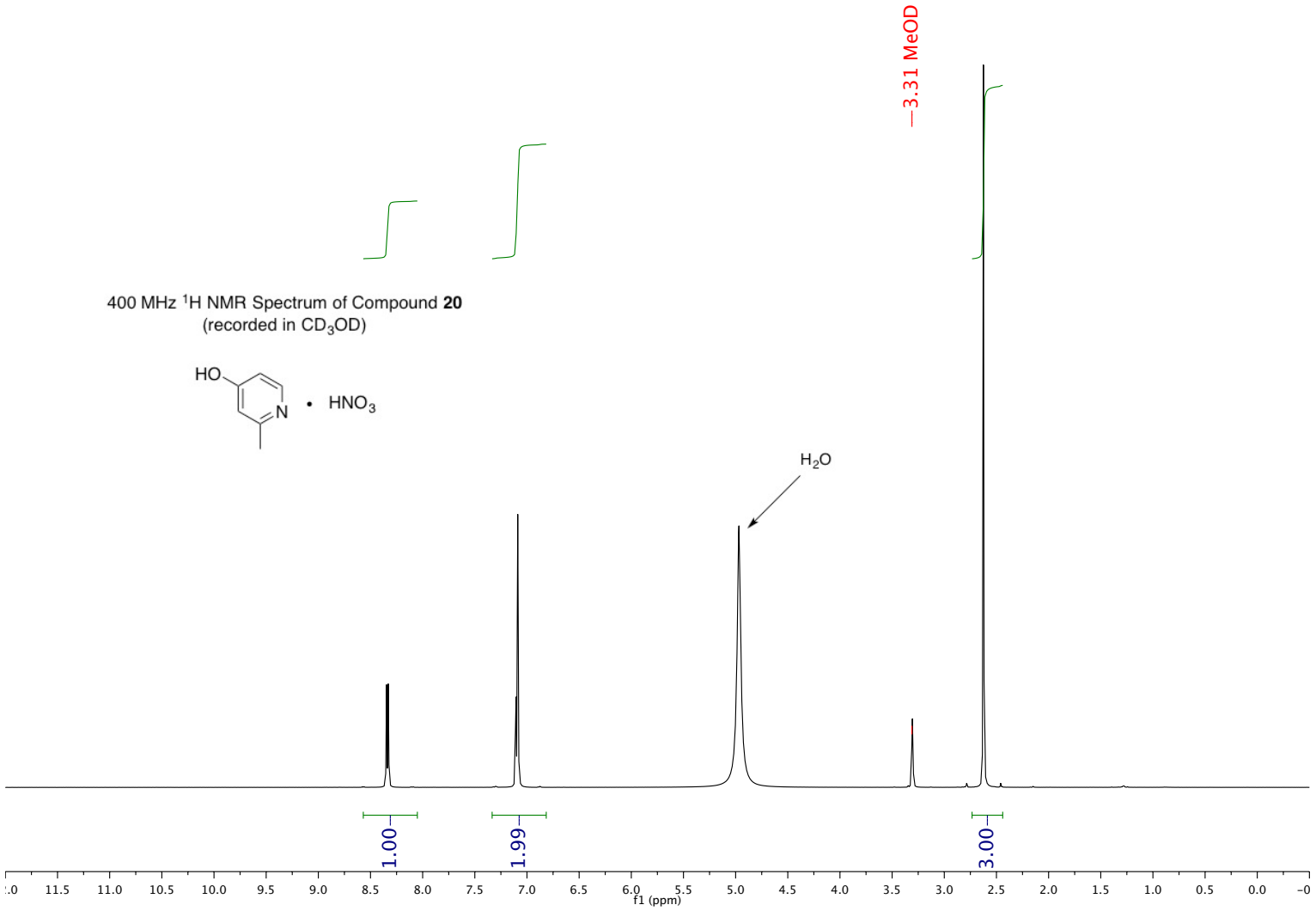

175 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in CD_3OD)
N
N
H
141.57
139.88
139.08
138.08
126.19
110.30
107.54
49.37 MeOD
49.24 MeOD
49.12 MeOD
49.00 MeOD
48.88 MeOD
48.76 MeOD
48.63 MeOD
24.20
24.06
23.87
21.61
24.20
24.06
23.87
25
24
23
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

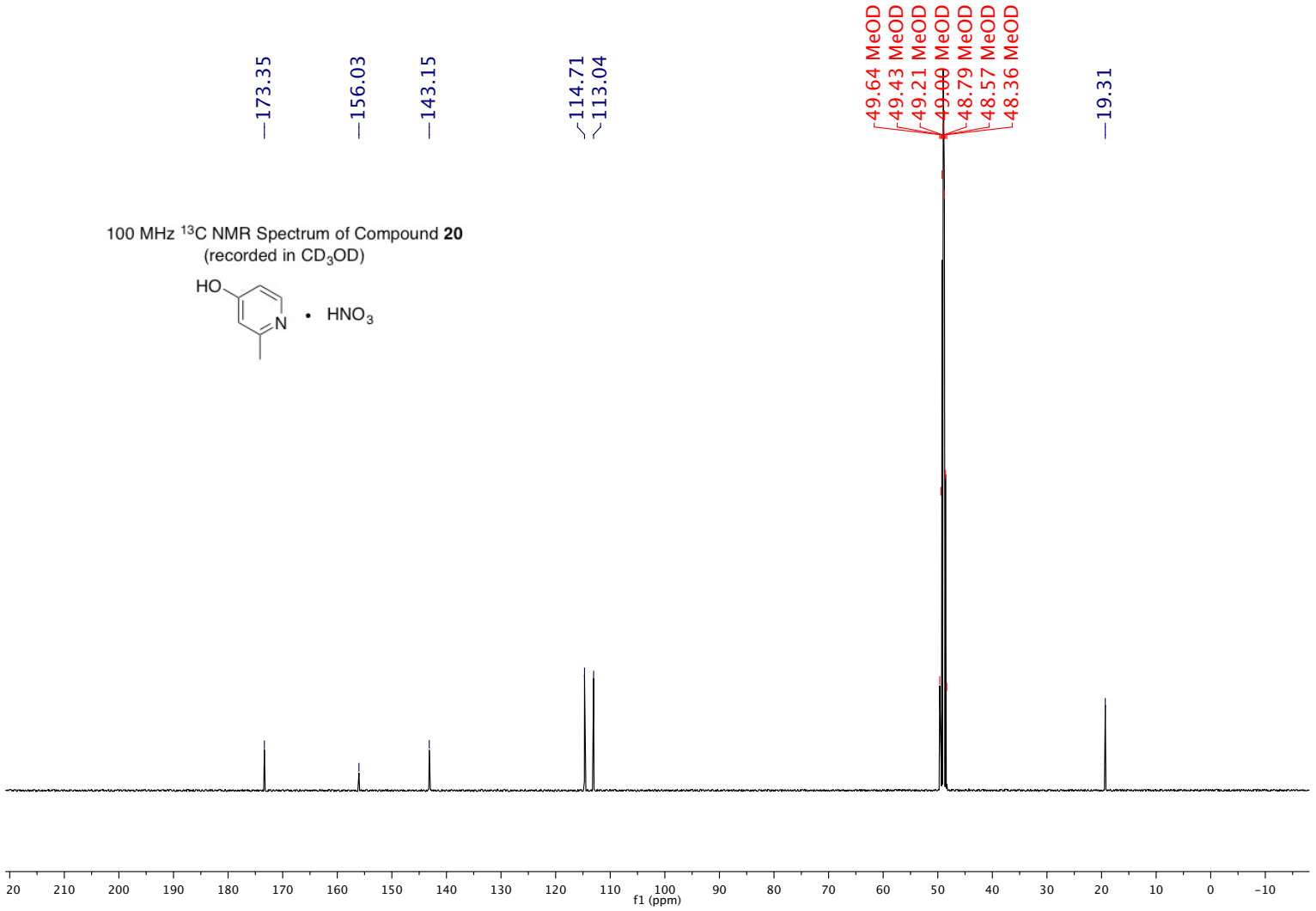

7.26 CDCl3
400 MHz ¹H NMR Spectrum of Compound 17
(recorded in CDCl3)
O
O2N
N
1.00
1.00
2.00
2.00
2.01
2.08
f1 (ppm)

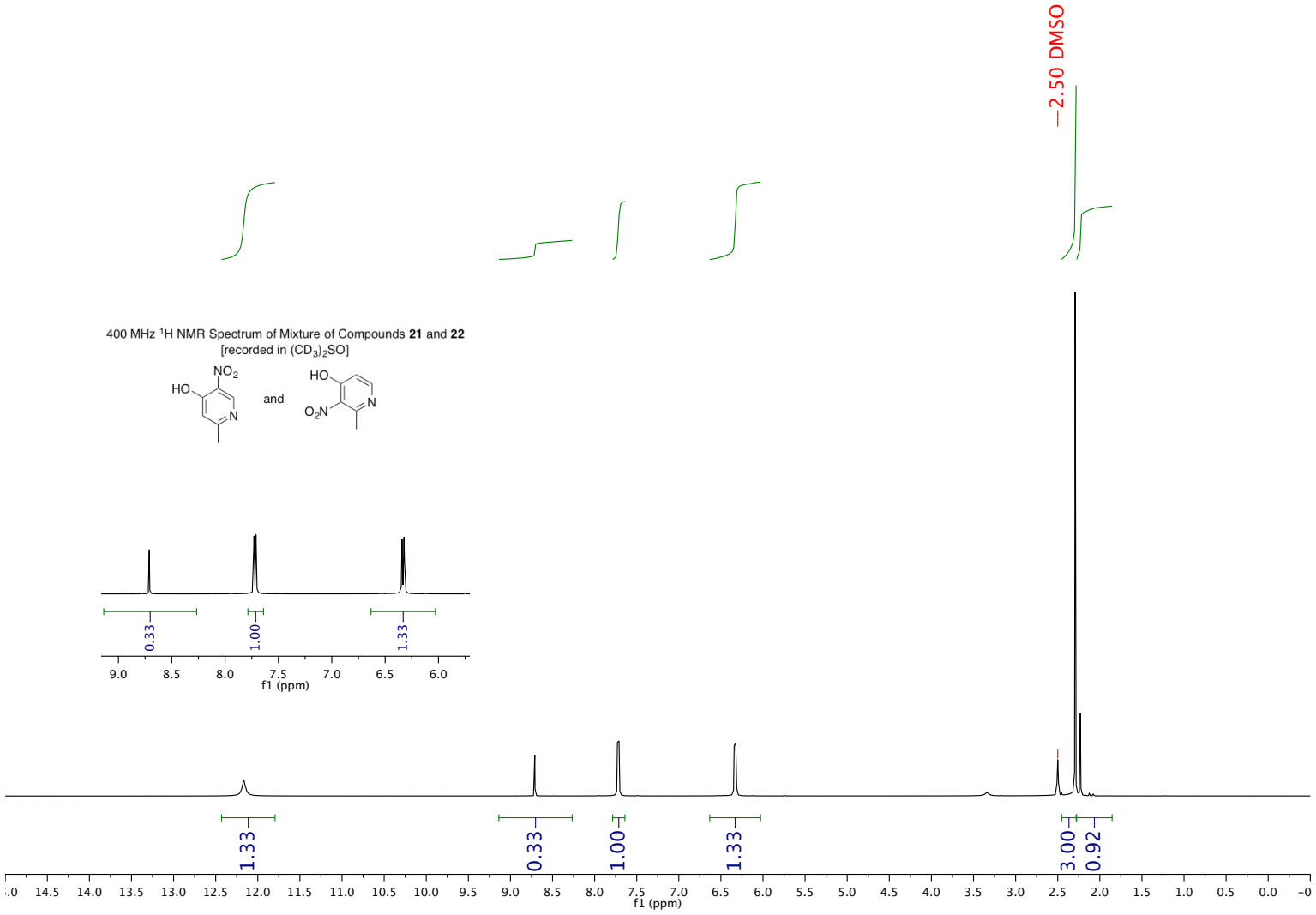

196.17
152.93
151.04
149.37
146.14
139.18
132.15
123.36
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.25
26.58
22.50
100 MHz 13C NMR Spectrum of Compound 17
(recorded in CDCl3)
N
O
O2N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

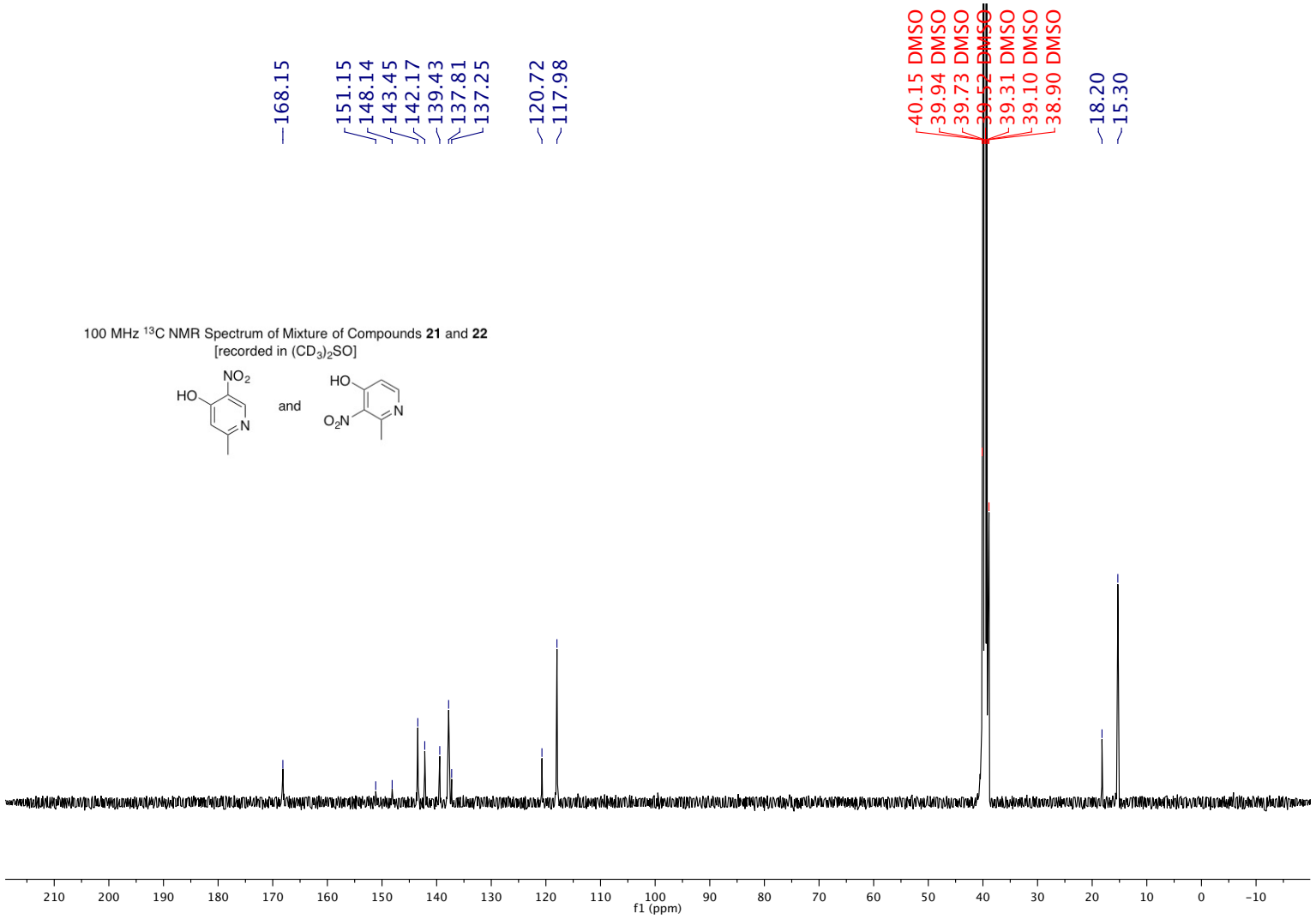

7.26 CDCl3
400 MHz ¹H NMR Spectrum of Compound 18
(recorded in CDCl3)
N
N
H
1.00
1.00
1.00
1.00
2.00
2.00
4.00
f1 (ppm)

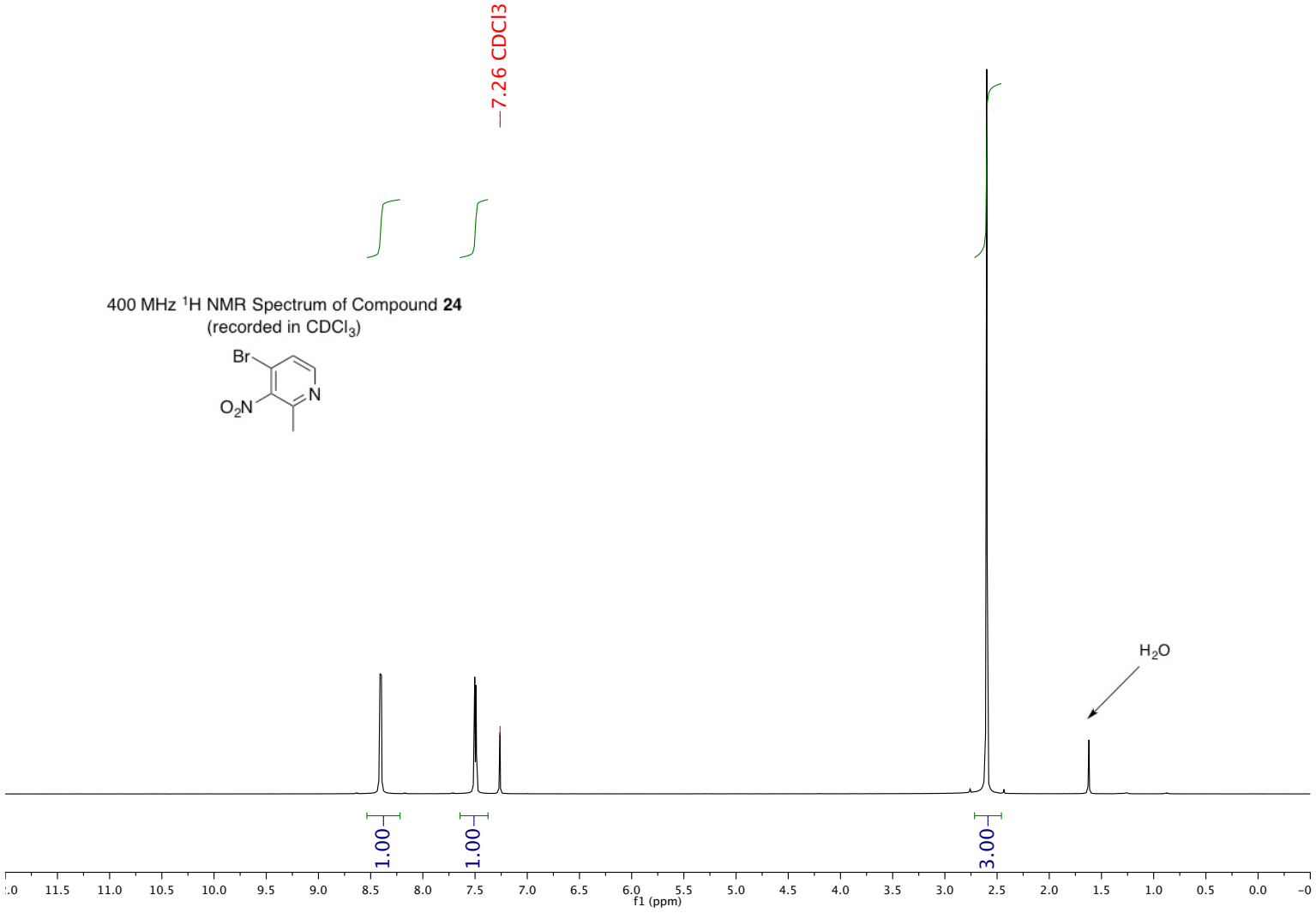

145.59
141.91
139.19
129.08
117.42
115.82
110.78
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
23.77
23.17
23.10
20.12
100 MHz 13C NMR Spectrum of Compound 18
(recorded in CDCl3)
N
N
H
23.77
23.17
23.10
24.0
23.5
23.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

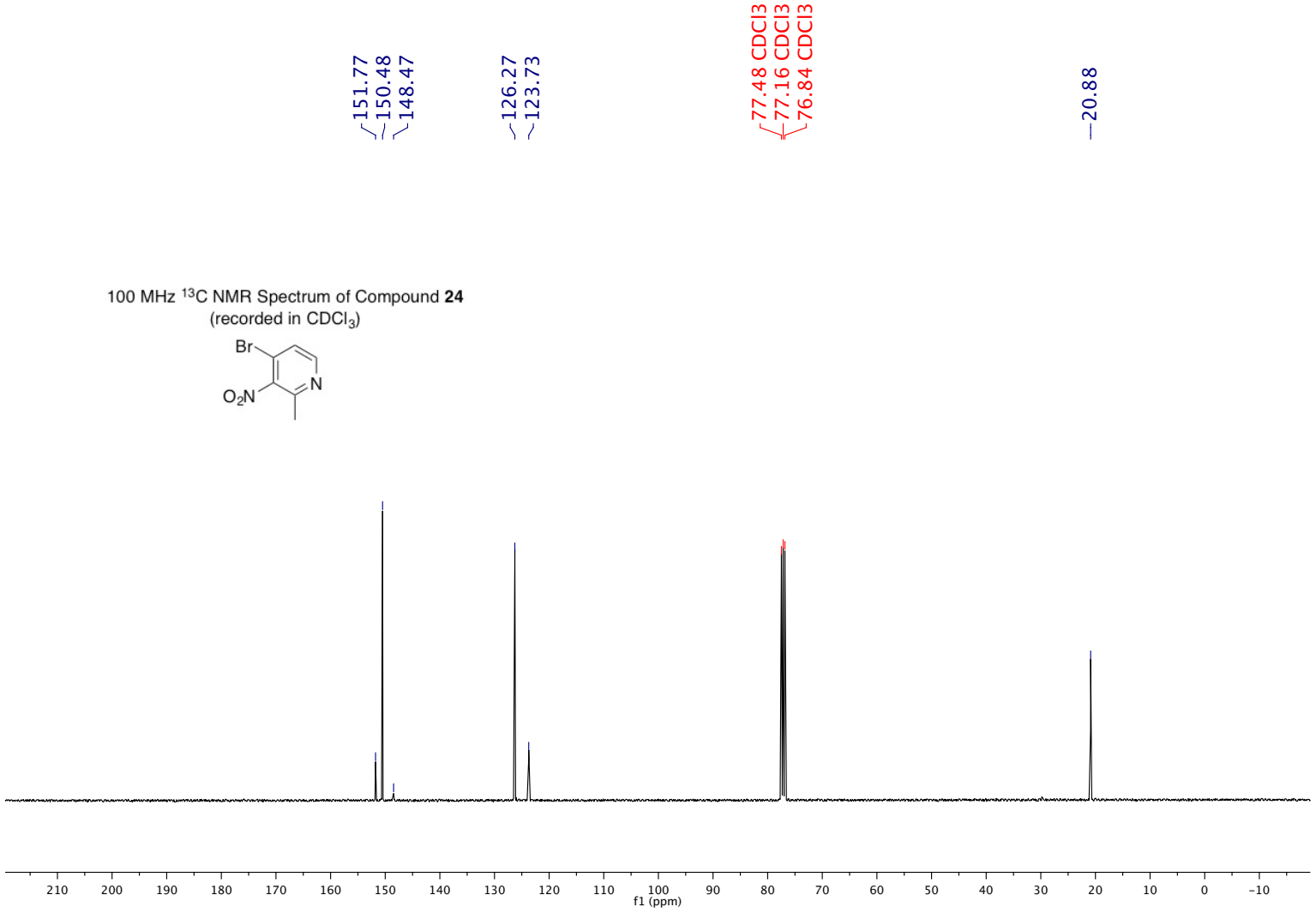

400 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in CD_3OD)
HO
N
• HNO_3
H_2O
3.31 MeOD
1.00
1.99
3.00
f1 (ppm)


173.35
156.03
143.15
114.71
113.04
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
19.31
100 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in CD_3OD)
HO
N
• HNO_3
f1 (ppm)


400 MHz ¹H NMR Spectrum of Mixture of Compounds 21 and 22
[recorded in (CD3)2SO]
NO2
HO
N
and
HO
O2N
N
2.50 DMSO
0.33
1.00
1.33
f1 (ppm)
1.33
0.33
1.00
1.33
3.00
0.92
f1 (ppm)

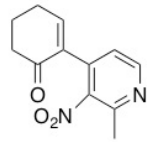

168.15
151.15
148.14
143.45
142.17
139.43
137.81
137.25
120.72
117.98
40.15 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.90 DMSO
18.20
15.30
100 MHz ^{13}C NMR Spectrum of Mixture of Compounds **21** and **22**
[recorded in $(CD_3)_2SO$]
HO
NO_2
N
and
HO
O_2N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

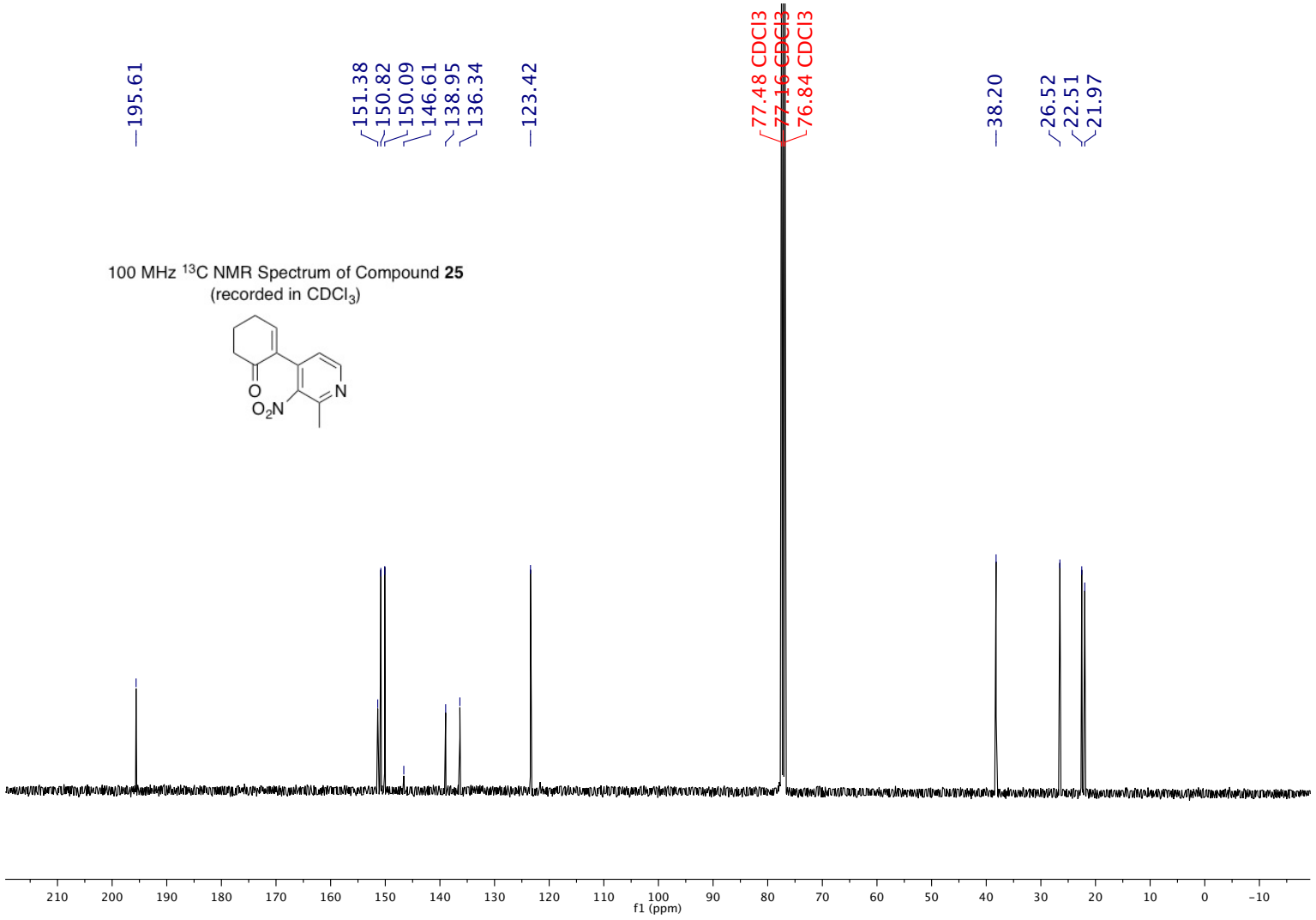

400 MHz ¹H NMR Spectrum of Compound 24
(recorded in CDCl3)
Br
O2N
N
7.26 CDCl3
H2O
1.00
1.00
3.00
f1 (ppm)

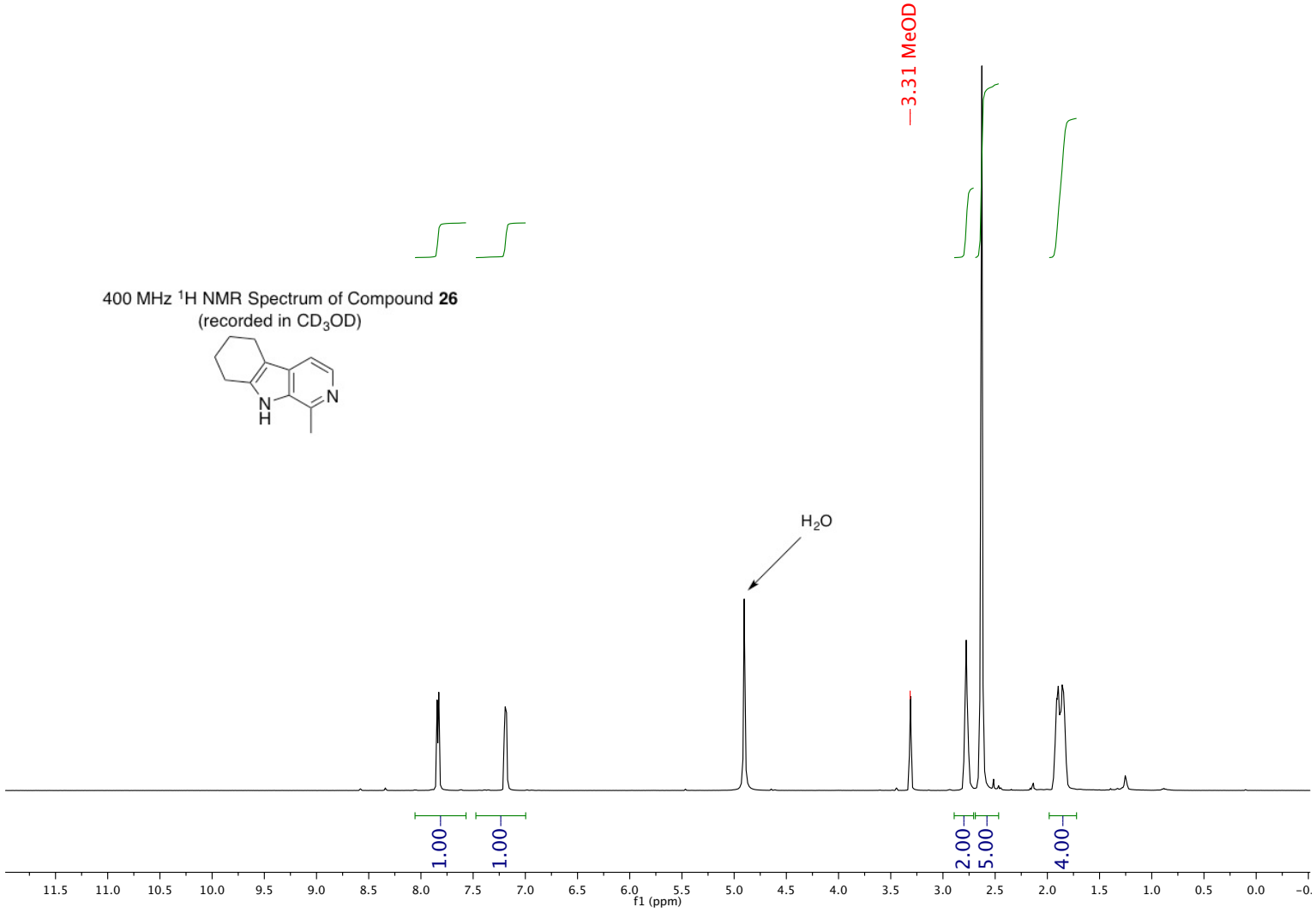


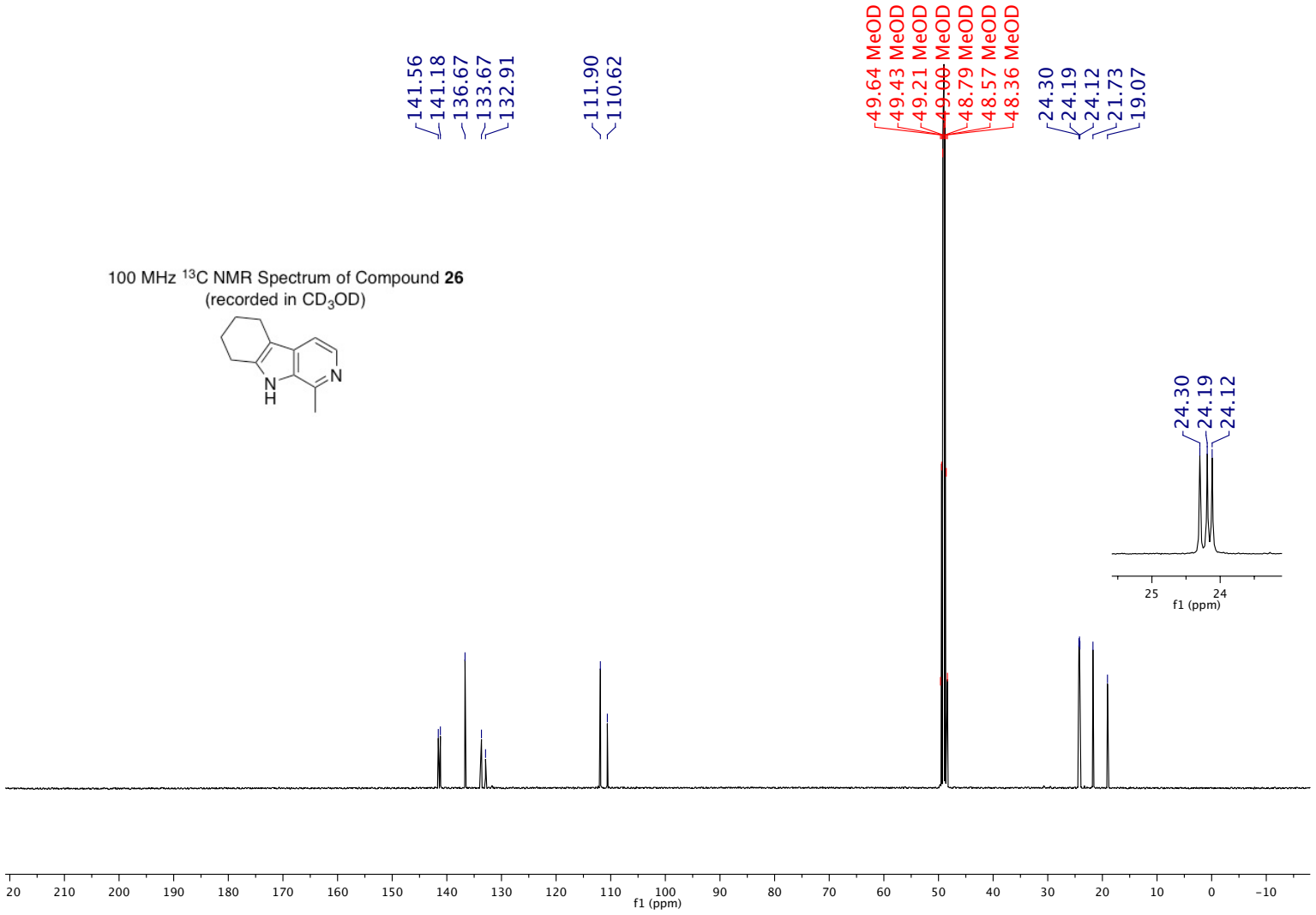
100 MHz ^{13}C NMR Spectrum of Compound **24**
(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **25**
(recorded in $CDCl_3$)




195.61
151.38
150.82
150.09
146.61
138.95
136.34
123.42
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.20
26.52
22.51
21.97
100 MHz 13C NMR Spectrum of Compound 25
(recorded in CDCl3)
O
O2N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


400 MHz ¹H NMR Spectrum of Compound 26
(recorded in CD3OD)
3.31 MeOD
H2O
1.00
1.00
2.00
5.00
4.00
f1 (ppm)


141.56
141.18
136.67
133.67
132.91
111.90
110.62
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
24.30
24.19
24.12
21.73
19.07
100 MHz 13C NMR Spectrum of Compound 26
(recorded in CD3OD)
N
H
N
24.30
24.19
24.12
25
24
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Appendix A

A Pd[0]-catalysed Ullmann Cross-coupling Route to Carbazoles

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Carbon-carbon bond-forming reactions, especially cross-coupling variants, are a central aspect of contemporary synthetic chemistry. The Ullmann reaction is a classic C–C bond forming process. The original form of this reaction was reported in 1901[1] and involves homo-coupling of two equivalents of an aryl halide in the presence of copper powder at high temperature to give corresponding and symmetrical biaryl. The Pd[0]-catalysed Ullmann cross-coupling reaction was first reported in 1993 by Shimizu and co-workers.[2] They used a range of Pd catalysts in combination with metallic copper and noted an attendant capacity to selectively form cross-coupling products under mild conditions.

Our group has reported[3] a Pd[0]-catalysed Ullmann cross-coupling approach to indoles that employs readily available starting materials and reagents (Figure 1). Significantly, it avoids the need to use organostannanes and addresses the regiochemical issues associated with the traditional Fischer indole synthesis. This presentation will detail extensions of such processes to the preparation of carbazoles including a range of natural products containing this ring system.

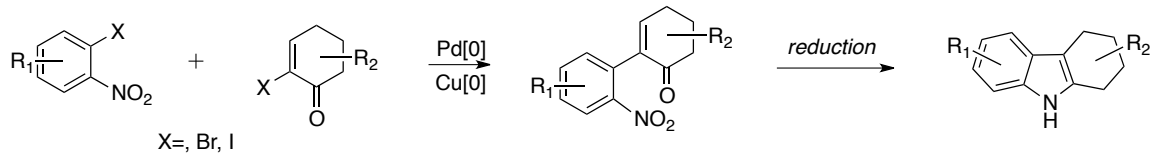

Figure 1 Pd[0]-catalysed Ullmann cross-coupling route to Indoles

[1] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, 108, 3054-3131.
[2] N. Shimizu, T. Kitamura, K. Watanabe, T. Yamaguchi, H. Shigyo, T. Ohta, *Tetrahedron Lett.* **1993**, 34, 3421-3424.
[3] M. G. Banwell, B. D. Kelly, O. J. Kokas, D. W. Lupton, *Org. Lett.* **2003**, 5, 2497-2500.

The Pd[0]-catalysed Ullmann Cross-coupling Route to Carbazoles

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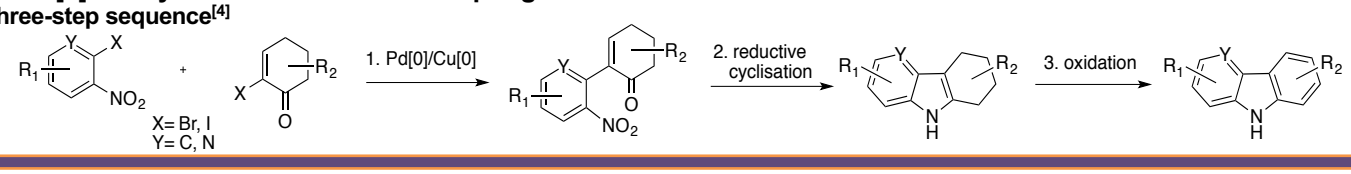
Introduction

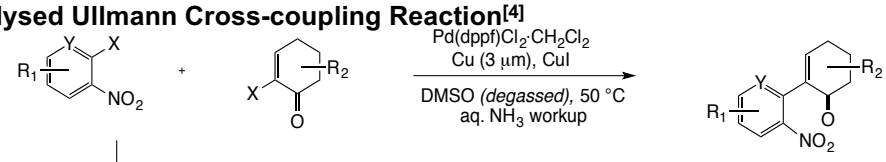
The Ullmann reaction is a classic C–C bond forming process. The original form of it was reported in 1901[1] and involves the homo-coupling of two equivalents of an aryl halide in the presence of copper powder at high temperature to give the corresponding, symmetrical biaryl. The Pd[0]-catalysed variant of the Ullmann cross-coupling reaction was first reported in 1993 by Shimizu and co-workers[2] who demonstrated the utility of this process for the selective formation of cross-coupled products under relatively mild conditions. This presentation will detail the application of the title process to the synthesis of carbazoles. Carbazole alkaloids are of great interest due to their diverse biological activities.[3] Indeed, certain carbazole–containing natural products show antitumor, antibacterial and/or antifungal properties as well as, in some instances, activity against malaria.

The Pd[0]-catalysed Ullmann Cross-coupling Route to Carbazoles

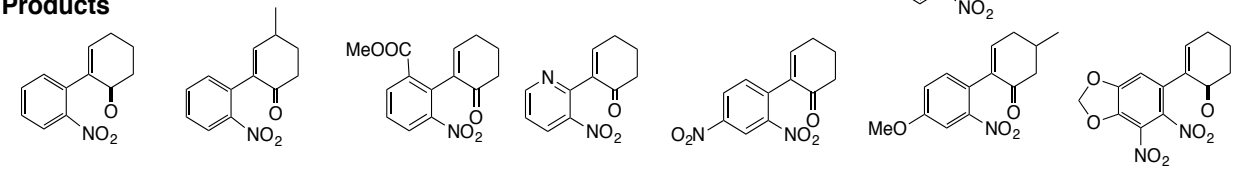
A three-step sequence[4]



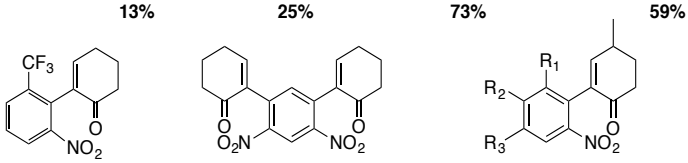
Step 1: The Pd[0]-catalysed Ullmann Cross-coupling Reaction[4]



Step 1: Products



69% 73% 13% 25% 73% 59% 32%

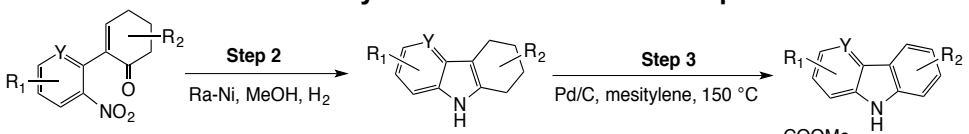


38% 33%

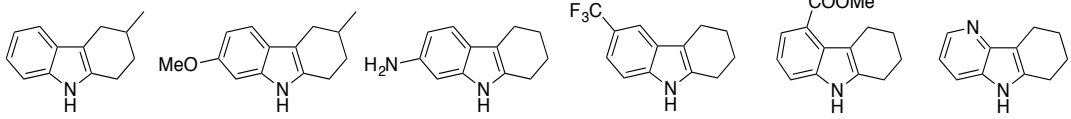
R_1 = OMe, R_2 = R_3 = H : **44%**
R_2 = OMe, R_1 = R_3 = H : **52%***
R_3 = OMe, R_1 = R_2 = H : **78%**

*Conditions: $Pd_2(dba)_3$, Cu bronze, DMSO, 50 °C

Steps 2 and 3: Carbazole Formation: Reductive Cyclisation and Oxidation Steps[5,6,7]

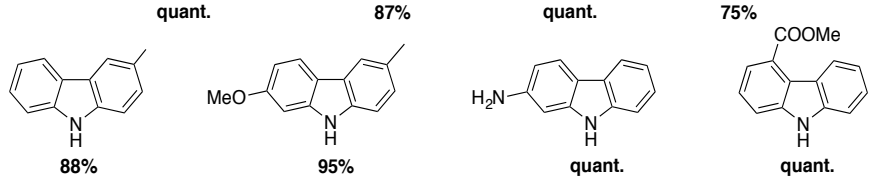


Step 2: Products



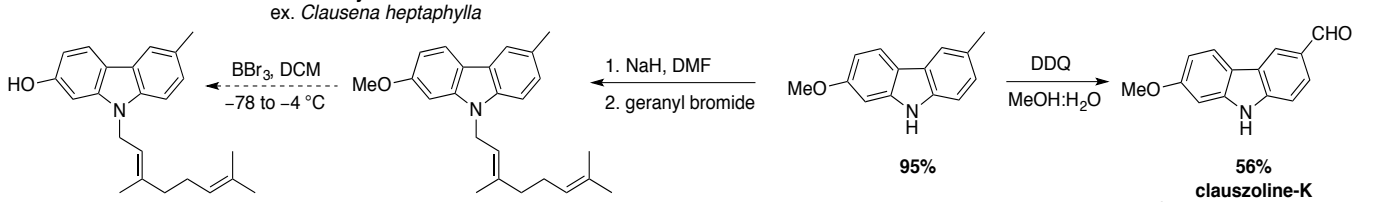
80% quant. 87% quant. 75% 14%

Step 3: Products



88% 95% quant. quant.

3-methylcarbazole
ex. *Clausena heptaphylla*



karapinchamine A
ex. Murraya Koenigii

quant. 95%

56%
clauszoline-K
ex. Clausena excavata BURM. F.

References

[1] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131.
[2] N. Shimizu, T. Kitamura, K. Watanabe, T. Yamaguchi, H. Shigyo, T. Ohta, *Tetrahedron Lett.* **1993**, *34*, 3421-3424.
[3] A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193-3328.
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